IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	**U.S. PATENT NO. 6,410,550**
ISSUED:	**JUNE 25, 2002**
TO:	**JOTHAM W. COE AND PAIGE R.P. BROOKS**
FOR:	**ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**
FROM:	**SERIAL NO. 09/402,010**
OF:	**Nov. 13, 1998**

Via Federal Express
Madison West Bldg.
600 Dulaney St. 7D-55
Alexandria, VA 22314

Attention: Mary Till

Madam:

TRANSMITTAL OF REPLACEMENT COPIES OF REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Enclosed are replacement copies of the application papers of PFIZER INC., dated June 28, 2006, for extension of the term of U.S. Patent No. 6,410,550 under 35 U.S.C. §156, based on the regulatory review period for CHANTIX™ (varenicline) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of five copies which were originally submitted June 28, 2006. A copy of the Postcard receipt stamped by USPTO Mail Room is also enclosed indicating receipt of the original papers by the USPTO on June 28, 2006.

Respectfully submitted,
PFIZER INC.

Date: October 24, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

Legal Division
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Facsimile Transmission

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To: Mary Till			
Location: Alexandria, Virginia			
Facsimile Telephone: 571-273-7755			
No. of Pages: (including this page) 2			
From: A. David Joran, Esq.			
Department Name:	**Legal Division**	**Charge No.:**	**88424**
Facsimile Telephone: (212) 573-1939			
Date: October 25, 2006		**Time (New York)** 4:13 PM	
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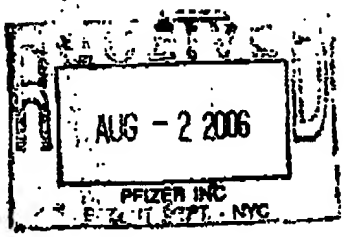
Note: Enclosed is the Postcard of PC10030A.



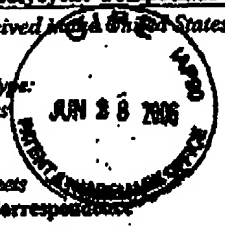
Date: June 28, 2006 Express Mail No. BY HAND

US Patent No. 6,410,550 Docket No. PC10030A By ADJ

Application of Jotham W. Coe et al Filing Date Nov. 13, 1998

Entitled Aryl Fused Azapolycyclic Compounds

The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:



- ☐ Application Transmittal *Type:*
- ☐ Specification *pages*
- ☐ Claims *pages*
- ☐ Abstract *pages*
- ☐ Drawing(s) *sheets*
- ☒ Power of Attorney and Correspondence Address Form
- ☒ Statement Under 37CFR 3.73 (b)
- ☒ Application for Extension of the Term of United States Patent No. 6,410,550 Under 35 U.S.C. §156
- ☒ Transmittal of Request for Extension of Patent Term Under 35 U.S.C. §156
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☒ EXHIBITS A through D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
TO:	JOTHAM W. COE AND PAIGE R.P. BROOKS
FOR:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
FROM:	SERIAL NO. 09/402,010
OF:	Nov. 13, 1998

Commissioner for Patents
Mail Stop Patent Ext.
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

TRANSMITTAL OF REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Transmitted herewith are the application papers of PFIZER INC., dated June 28, 2006, for extension of the term of U.S. Patent No. 6,410,550 under 35 U.S.C. §156, based on the regulatory review period for CHANTIX™ (varenicline) Tablets, together with two duplicate copies as required under 37 C.F.R. §1.740(b) and two additional duplicate copies of the application pursuant to M.P.E.P. §2753, for a total of four copies and one original.

As set forth under 37 C.F.R. §1.20(j), please charge the sum of $1,120.00 to Deposit Account No. 16-1445 for the filing of this application for extension of patent term. Also, please charge any underpayment, or any additional fees that may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,
PFIZER INC.

Date: June 28, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
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Respectfully submitted,
PFIZER INC.

Date: June 28, 2006

A. David Joran
Attorney for Applicant
Reg. No. 37,858

PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755
Tel.: (212) 733-3381
Fax: (212) 573-1939

PTO/SB/96 (12-05)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Pfizer Inc.

Application No./Patent No./Control No.: 09/402,010 Filed/Issue Date: September 28, 1999

Entitled: ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

Pfizer Inc, a Corporation
(Name of Assignee) (Type of Assignee: corporation, partnership, university, government agency, etc.)

states that it is:

1. ☑ the assignee of the entire right, title, and interest; or

2. ☐ an assignee of less than the entire right, title and interest
(The extent (by percentage) of its ownership interest is _____%)

in the patent application/patent identified above by virtue of either:

A. ☑ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 012920, Frame 0128, or a true copy of the original assignment is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Grover F. Fuller Jr.

Signature | Date

Grover F. Fuller Jr., Reg. No. 31,760 | (212)-573-1390

Printed or Typed Name | Telephone Number

Senior Corporate Counsel of Pfizer Inc

Title

PTO/SB/81 (01-06)
Approved for use through 12/31/2008. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	09/402,010
Filing Date	September 28, 1999
First Named Inventor	Jotham Wadsworth Coe
Title	ARYL FUSED AZAPOLYCYCLIC COMPOUN
Art Unit	
Examiner Name	
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 23913

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☑ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

☑ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature	Grover F. Fuller	Date	
Name	Grover F. Fuller Jr., Reg. No. 31,760	Telephone	212-573-1390
Title and Company	Senior Corporate Counsel of Pfizer Inc		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S. PATENT NO. 6,410,550
ISSUED:	JUNE 25, 2002
TO:	JOTHAM W. COE AND PAIGE R.P. BROOKS
FOR:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
FROM:	SERIAL NO. 09/402,010
OF:	Nov. 13, 1998

Commissioner for Patents
Mail Stop Patent Extension
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 6,410,550 UNDER 35 U.S.C. §156 FOR CHANTIX™ (VARENICLINE) TABLETS

Your applicant, PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 235 East 42nd Street, New York, NY 10017, United States of America, represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 6,410,550 granted to JOTHAM W. COE and PAIGE R.P. BROOKS on the 25th day of June, 2002, for ARYL FUSED AZAPOLYCYCLIC COMPOUNDS, by virtue of assignments, recorded in the United States Patent and Trademark Office (hereinafter referred to as "the Patent Office") on the 20th day of May, 2002 at Reel 012920, Frame 0128. A copy of the Notice of Recordation is enclosed as Exhibit A.

Pursuant to the provisions of 37 C.F.R. §1.730, your applicant hereby applies for an extension of the term of Patent No. 6,410,550 under 35 U.S.C. §156 of 545 days, based on the materials set forth herein and in the accompanying papers.

In the materials which follow herein, numbered paragraphs (1) through (15) correspond to paragraphs (1) through (15) of 37 C.F.R. §1.740(a).

(1) The approved product is the active ingredient, including any salt of the active ingredient, in CHANTIX™, *i.e.,* varenicline, varenicline tartrate, and any other pharmaceutically acceptable salt of varenicline, which is the generic name of the chemical compound. CHANTIX™ tablets consist of varenicline as the varenicline tartrate salt and pharmaceutically-acceptable carriers. Varenicline and varenicline tartrate are further identified as follows:

Varenicline:

Chemical Name

7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine

Alternate Chemical Name

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene

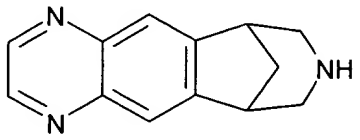
Molecular Formula

$C_{13}H_{13}N_3$

Molecular Weight

211.27

Chemical Formula



Varenicline tartrate:

Chemical Name

7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1)

Alternate Chemical Name

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate

Molecular Formula

$C_{13}H_{13}N_3 \bullet C_4H_6O_6$

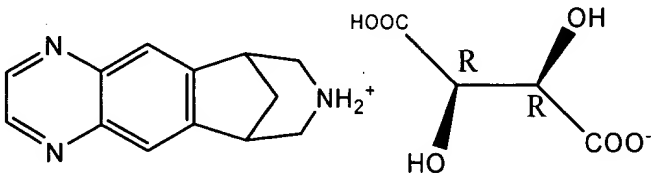
Molecular Weight

361.35

Physical Description

CHANTIX™ tablets are supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablets debossed with *"Pfizer"* on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1mg CHANTIX™ tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

Chemical Formula



(2) CHANTIX™ (varenicline) tablets was subject to regulatory review under section 505(b) of the Federal Food, Drug and Cosmetic Act, which is codified at 21 U.S.C. §355(b).

(3) CHANTIX™ (varenicline) tablets received permission for commercial marketing or use under section 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355(b), on May 10, 2006. It was approved as an aid to smoking cessation treatment.

(4) The active ingredient in CHANTIX™ tablets is varenicline, as its salt varenicline tartrate (5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene tartrate). Neither varenicline nor any salt thereof has been previously approved for

commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application could be submitted is July 10, 2006.

(6) The patent for which an extension is being sought is identified as follows:

Inventors:	JOTHAM W. COE AND PAIGE R.P. BROOKS
Patent No.:	6,410,550
For:	ARYL FUSED AZAPOLYCYCLIC COMPOUNDS
Issued:	JUNE 25, 2002
Expires:	NOVEMBER 13, 2018

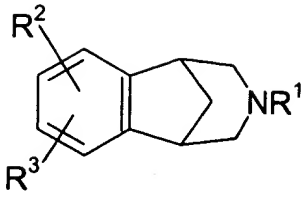
(7) A copy of Patent No. 6,410,550, the patent for which an extension is being sought, is attached hereto as EXHIBIT B.

(8) A maintenance fee payment for Patent No. 6,410,550 has been made to keep the patent in force beyond four years from its issue date. A copy of the official receipt for such payment is attached hereto as EXHIBIT C. Patent No. 6,410,550 has no disclaimers or re-examination certificates.

(9) Patent No. 6,410,550 claims the approved product, pharmaceutical compositions including the approved product, and a method of using the approved product. Claims 1 and 8 claim the approved product *per se*; claim 12 claims a pharmaceutical composition which contains the approved product and is useful for the approved use; and, claims 13 and 14 claim the approved use of the approved product. A showing that lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product, a pharmaceutical composition containing the approved product, or a method of using the approved product is as follows:

Claim 1 of Patent No. 6,410,550 reads as follows:

" A compound of the formula



(I)

R^1 is hydrogen, $(C_1\text{-}C_6)$alkyl, unconjugated $(C_3\text{-}C_6)$alkenyl, $XC(=O)R^{13}$, benzyl or $-CH_2CH_2\text{-}O\text{-}(C_1\text{-}C_4)$alkyl;

R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from $(C_1\text{-}C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1\text{-}C_6)$alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, hydroxy, amino, $(C_1\text{-}C_6)$alkylamino and $((C_1\text{-}C_6)\text{alkyl})_2$amino, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ and $-XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1\text{-}C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, -N-$(C_1\text{-}C_6)$alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1\text{-}C_6)$alkylene;

or a pharmaceutically acceptable salt thereof."

When R_1 is hydrogen; and, R^2 and R^3, together with the carbons to which they are attached, form a six-membered monocyclic carbocyclic ring that is unsaturated, wherein two of the nonfused carbon atoms of said monocyclic ring are replaced by a nitrogen, and wherein the monocyclic ring is not substituted, the compound claimed is varenicline. Therefore, claim 1 reads on the approved product.

Claim 8 of Patent No. 6,410,550 claims the compound according to claim 1 which is 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene, which is varenicline. Claim 8 also claims a pharmaceutically acceptable salt 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene, which encompasses varenicline tartrate. Therefore, claim 8 reads on the approved product.

Claim 12 of Patent No. 6,410,550 claims a pharmaceutical composition comprising an amount of a compound according to claim 1 and a pharmaceutically acceptable carrier. Since claim 1 claims a compound which encompasses varenicline, claim 12 reads on a pharmaceutical composition comprising the approved product.

Claim 13 of Patent No. 6,410,550 claims a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim 1 that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use. Since claim 1 claims a compound which encompasses varenicline, claim 8 reads on a method of using the approved product for the approved use.

Claim 14 of Patent No. 6,410,550 claims a method for treating a disorder or condition selected from a grouping of indications which recites dependencies on, or addictions to, nicotine and tobacco products, comprising administering to a mammal in need of such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition. Since claim 1 claims a compound which encompasses varenicline, claim 14 reads on a method of using the approved product for the approved use.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for varenicline tartrate October 14, 1999, following receipt by the Food and Drug Administration of Investigational New Drug ("IND") Application No. 58,994 on September 15, 1999.
- A New Drug Application ("NDA") under section 505(b) of the Federal Food, Drug and Cosmetic Act for CHANTIX™ was initially submitted on November 10, 2005, as NDA No. 21-928.
- NDA No. 21-928 was approved on May 10, 2006.

(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as EXHIBIT D.

(12) Applicant is of the opinion that Patent No. 6,410,550 is eligible for an extension under 35 U.S.C. §156. The length of extension claimed is 545 days.

The eligibility requirements of 35 U.S.C. §§156(a) and 156(c)(4) have been satisfied as follows:

- Patent No. 6,410,550 claims a product (the active ingredient, including any salt of the active ingredient) in CHANTIX™, *i.e.,* varenicline, varenicline tartrate and any other pharmaceutically acceptable salt. Patent No. 6,410,550 also claims pharmaceutical compositions including the product CHANTIX™ and a method of using the product CHANTIX™.
- Patent No. 6,410,550 is currently set to expire on November 13, 2018 (*i.e.,* the term of the patent has not yet expired).
- The term of Patent No. 6,410,550 has never been extended under subsection (e)(1) of 35 U.S.C. §156.
- This application for extension is being submitted by PFIZER INC, the owner of record of Patent No. 6,410,550, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d).
- The product (the active ingredient, including any salt of the active ingredient) in CHANTIX™, *i.e.,* varenicline, varenicline tartrate and any other pharmaceutically acceptable salt, has been subject to a regulatory review period under section 505(b) of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and the permission for said commercial marketing or use is the first permitted commercial marketing or use of the product under section 505(b) of the Federal Food, Drug and Cosmetic Act.
- No patent has to this date been extended, nor has any other extension been applied for, under subsection (e)(1) of 35 U.S.C. §156, for the regulatory review period which forms the basis for this application for extension of the term of Patent No. 6,410,550.

The length of extension of the term of Patent No. 6,410,550 of 545 days claimed by applicant was determined according to the provisions of 37 C.F.R. §1.775 as follows:

- According to 37 C.F.R. §1.775(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.775.
- According to 37 C.F.R. §1.775(c), the regulatory review period is the sum of: (A) the number of days in the period beginning on the date the exemption under subsection 505 of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act; and (B) the number of days in the period beginning on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act and ending on the date the NDA was approved. The exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective on October 14, 1999; the NDA was initially submitted on November 10, 2005; and the NDA was approved on May 10, 2006. Hence, the regulatory review period under 37 C.F.R. §1.775(c) is the sum of the period from October 14, 1999 to November 10, 2005 and from November 10, 2005 to May 10, 2006. This is the sum of 2,219 days and 180 days, which is 2,399 days.
- According to 37 C.F.R. §1.775(d)(1)(i), the number of days in the regulatory review period which were on and before the date on which the patent issued must be subtracted. Patent No. 6,410,550 issued on June 25, 2002. Subtraction of the period on and before June 25, 2002 leaves a reduced regulatory review period from June 26, 2002 to November 10, 2005 and from November 10, 2005 to May 10, 2006. This is the sum of 1,234 days and 180 days, which is 1,414 days.
- 37 C.F.R. §1.775(d)(1)(ii) does not apply.
- According to 37 C.F.R. §1.775(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. §1.775(c)(1). This is one-half of 1,234 days, which is 617 days. After subtraction, this now leaves a reduced regulatory review period of 617 days plus 180 days, which is 797 days.

- According to 37 C.F.R. §1.775(d)(2), the reduced regulatory review period of 797 days must be added to the expiration date of Patent No. 6,410,550 (*i.e.*, November 13, 2018). This gives a date of July 22, 2020. According to 37 C.F.R. §1.775(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of May 10, 2020. According to 37 C.F.R. §1.775(d)(4), the earlier of these dates must be selected. The earlier of these dates is May 10, 2020 (*i.e.*, 545 days beyond the expiration date of the 6,410,550 patent).
- The provisions of 37 C.F.R. §1.775(d)(5) apply to this application, because Patent No. 6,410,550 issued after September 24, 1984. Pursuant to 37 C.F.R. §1.775(d)(5)(i) five (5) years are added to the expiration date of Patent No. 6,410,550 (November 13, 2018) giving a date of November 13, 2023. According to 37 C.F.R. §1.775(d)(5)(ii), the dates obtained pursuant to 37 C.F.R. §1.775(d)(5)(i) and 37 C.F.R. §1.775(d)(4) are compared and the earlier date is selected. The date calculated according to 37 C.F.R. §1.775(d)(4) above is May 10, 2020. Therefore, the earlier of these dates is May 10, 2020. Applicant is entitled to an extension of term of Patent No. 6,410,550 until May 10, 2020, *i.e.*, an extension of 545 days from the original expiration date of November 13, 2018.
- 37 C.F.R. §1.775(d)(6) does not apply because Patent No. 6,410,550 issued on June 25, 2002, after September 24, 1984.

(13) Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension of 545 days which is being sought to the term of Patent No. 6,410,550.

(14) The prescribed fee under 37 C.F.R. §1.20(j) for receiving and acting on this application for patent term extension is to be charged to Deposit Account No. 16-1445, as requested in the enclosed transmittal letter.

(15) Please direct all inquiries and correspondence relating to this application for patent term extension as follows:

(16)

A. David Joran
PFIZER INC.
Legal Division
150 East 42nd Street
New York, NY 10017-5755

Tel: (212) 733-3381
Fax: (212) 573-1939

Pursuant to 37 C.F.R. §1.740(b), two duplicate copies of these application papers are enclosed herewith. Pursuant to M.P.E.P. §2753 an additional two copies of the application are also enclosed herewith. Accordingly, a total of four copies of the application and one original application for patent term extension of Patent No. 6,410,550 are submitted herewith.

Applicant respectfully requests prompt and favorable action on the merits of this application for extension of the term of Letters Patent No. 6,410,550 of 545 days, based on the regulatory review period for CHANTIX™ (varenicline) Tablets.

Respectfully submitted,
PFIZER INC

Date: June 28, 2006

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UNITED STATES PATENT AND TRADEMARK OFFICE

JULY 25, 2002

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Chief Information Officer
Washington, DC 20231
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PFIZER INC
PAUL H. GINSBURG
150 EAST 42ND STREET (150/05/49)
NEW YORK, NY 10017-5612

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RECORDATION DATE: 05/20/2002

REEL/FRAME: 012920/0128
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
COE, JOTHAM WADSWORTH

DOC DATE: 05/06/2002

ASSIGNOR:
BROOKS, PAIGE ROANNE PALMER

DOC DATE: 05/06/2002

ASSIGNEE:
PFIZER INC.
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SERIAL NUMBER: 09402010
PATENT NUMBER: 6410550

FILING DATE: 09/28/1999
ISSUE DATE: 06/25/2002

KIMBERLY WHITE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

05-28-2002

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FORM PTO-1595 1-31-92	RECORDATION PAT	DEPARTMENT OF COMMERCE Patent and Trademark

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Jotham Wadsworth Coe
Paige Roanne Palmer Brooks 5-20-02

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Pfizer Inc. MAY 20 2002
Street Address: 235 East 42nd Street

City: New York State: New York Zip: 10017-5755

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
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☐ Other _____

Execution Date: MAY 6, 2002

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s) B. Patent No. (s)
U.S. Ser. No. 09/402,010

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Paul H. Ginsburg
Internal Address: Pfizer Inc
Street Address: 150 East 42nd Street (150/05/49)
City: New York State: New York ZIP: 10017-5612

6. Total number of pages including cover sheet, attachments and document: 4

7. Total fee (37 CFR 3.41).....$ 40.00

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Name of Person Signing	Signature	Date

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CONFORMS WITH FORM PTO-1595

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ASSIGNMENT

For valuable consideration, the receipt and adequacy of which is hereby acknowledged, we, **Jothan Wadsworth COE and Paige Roanne Palmer BROOKS** of **8 Bush Hill Drive, Niantic, Connecticut 06357, United States of America and 9 Wyassup Road, North Stonington, Connecticut 06359, United States of America** respectively, hereby sell, assign and transfer unto PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, United States of America, and having its principal place of business at 235 East 42nd Street, New York, New York 10017, United States of America, our entire right, title and interest, except as limited hereinbelow, in and to patent application of the United States of America, having PFIZER INC. Docket No. PC 10030A, entitled **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**; filed in the United States Patent and Trademark Office on **September 28, 1999** and assigned application number **09/402,010**; and our entire right, title and interest, in the United States of America, in and to all our inventions, whether joint or sole, disclosed in said patent application; and our entire right, title and interest in and to all applications filed in the United States of America for Letters Patent for any or all of said inventions; and our entire right, title and interest in and to all Letters Patent granted in the United States of America on the foregoing applications;

and we hereby sell, assign and transfer unto PFIZER PRODUCTS INC., a corporation organized and existing under the laws of the State of Connecticut, United States of America, and having its place of business at Eastern Point Road, Groton, Connecticut 06340, United States of America, our entire right, title and interest, in all countries of the world except the United States of America, in and to all our inventions, whether joint or sole, disclosed in said patent application; and our entire right, title and interest in and to all patent applications filed outside the United States of America for Letters Patent for any or all of said inventions; and our entire right, title and interest in and to all Letters Patent granted outside the United States of America on said patent applications filed outside the United States of America; and the right to claim priority from said patent application under the Paris Convention for the Protection of Industrial Property, and under any and all other such treaties and agreements to which the United

States of America is a party and which afford similar priority-claiming privileges, in all countries of the world except the United States of America;

and we hereby agree, whenever requested, to communicate to said PFIZER INC. and said PFIZER PRODUCTS INC., and their successors and assigns, any facts known to us respecting said inventions, to testify in any legal proceeding respecting said inventions, and to execute all applications or papers necessary to obtain and maintain proper patent protection on said inventions in all countries of the world.

Signed and witnessed this 6th Day of MAY 2002

at **Groton, Connecticut, USA**

Jotham Wadsworth Coe

Jotham Wadsworth COE

In the presence of:

Martin Patrick Allen

Martin Patrick Allen

(Typed or Printed Name of Witness)

Signed and witnessed this 6th Day of MAY 2002

at **Groton, Connecticut, USA**

Paige Roanne Palmer Brooks

Paige Roanne Palmer BROOKS

In the presence of:

Krista Entrop Bianco

Krista Entrop Bianco

(Typed or Printed Name of Witness)

US006410550B1

(12) **United States Patent**
Coe et al.

(10) **Patent No.: US 6,410,550 B1**
(45) **Date of Patent: Jun. 25, 2002**

(54) **ARYL FUSED AZAPOLYCYCLIC COMPOUNDS**

(75) Inventors: **Jotham Wadsworth Coe**, Niantic; **Paige Roanne Palmer Brooks**, North Stonington, both of CT (US)

(73) Assignee: **Pfizer INC**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/402,010**

(22) PCT Filed: **Nov. 13, 1998**

(86) PCT No.: **PCT/IB98/01813**

§ 371 (c)(1),
(2), (4) Date: **Sep. 28, 1999**

(87) PCT Pub. No.: **WO99/35131**

PCT Pub. Date: **Jul. 15, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/070,245, filed on Dec. 31, 1997.

(51) **Int. Cl.**[7] **A61K 31/44**; A61K 31/505; C07D 221/22; C07D 413/00; A61P 1/00

(52) **U.S. Cl.** **514/289**; 514/210.21; 514/228.2; 514/232.8; 514/253.02; 514/253.03; 514/256; 514/281; 514/295; 546/43; 546/74; 546/97; 544/58.2; 544/60; 544/125; 544/126; 544/242; 544/361

(58) **Field of Search** 546/43, 74, 97; 544/58.2, 60, 125, 126, 242, 361; 514/210.21, 228.2, 232.8, 253.02, 253.03, 256, 281, 289, 295

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,471,503 A * 10/1969 Carson 260/294.7

FOREIGN PATENT DOCUMENTS

EP	0 955 301	* 11/1999
EP	1 078 637	* 2/2001
WO	WO 99/55680	* 11/1999
WO	WO 00/44755	* 8/2000
WO	WO 00/45846	* 8/2000

OTHER PUBLICATIONS

Mazzocchi et al., Synthesis and Pharmacological Activity of 2,3,4,5–Tetrahydro1,5 methano–1H–3–benzazepines, Journal of Medicinal Chemistry, vol. 22, No. 4, pp. 455–457, 1979.*

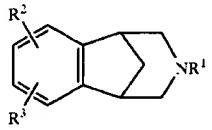
* cited by examiner

Primary Examiner—Brenda Coleman
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Paul H. Ginsburg; Roy F. Waldron

(57) **ABSTRACT**

Compounds of the formula

(I)



and their pharmaceutically acceptable salts, wherein R^1, R^2, and R^3 are defined as in the specification, intermediates in the synthesis of such compounds. pharmaceutical compositions containing such compounds and methods of using such compounds, in the treatment of neurological and psychological disorders.

15 Claims, No Drawings

ARYL FUSED AZAPOLYCYCLIC COMPOUNDS

This application is a national stage entry under 35 U.S.C. §371 of PCT/IB98/01813, filed Nov. 13, 1998 which claims the benefit of U.S. Provisional Application Ser. No. 60/070,245, filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds, as defined more specifically by formula I below. Compounds of formula I bind to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Such compounds are useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac, arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder, psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

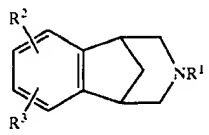
The compounds of this invention may also be used in combination with an antidepressant such as, for example, a tricyclic antidepressant or a serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's Chorea or traumatic brain injury (TBI): in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD, stroke, Huntington's Chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age related cognitive decline, AD, PD stroke, Huntington's Chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal antiinflammatory agents and estrogen-like therapy.

Other compounds that bind to neuronal nicotinic receptor sites are referred to in U.S. patent application Ser. No. 08/963,852, which was filed on Nov. 4, 1997 now U.S. Pat. No. 6,020,335. The foregoing application is owned in common with the present application, and is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

This invention relates to aryl fused azapolycyclic compounds of the formula

(I)



R^1 is hydrogen, $(C_1–C_6)$alkyl, unconjugated $(C_3–C_6)$ alkenyl, benzyl, $XC(=O)R^{13}$ or $—CH_2CH_2—O—(C_1–C_4)$alkyl;

R^2 and R^3 are selected, independently, from hydrogen, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, amino, halo, cyano, $—SO_q(C_1–C_6)$alkyl wherein q is zero, one or two, $(C_1–C_6)$alkylamino-, $[(C_1–C_6)$alkyl$]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ $—XC(=O)R^{13}$, aryl-$(C_0–C_3)$alkyl- or aryl-$(C_0–C_3)$alkyl-O—, wherein said aryl is selected from phenyl and naphthyl, heteroaryl-$(C_0–C_3)$alkyl- or heteroaryl-$(C_0–C_3)$alkyl-O—, wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein X^2 is absent or X^2 is $(C_1–C_6)$ alkylamino- or $[(C_1–C_6)$alkyl$]_2$amino-, and wherein the $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety of said $X^2(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- contains at least one carbon atom, and wherein from one to three of the carbon atoms of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- moiety may optionally be replaced by an oxygen, nitrogen or sulfur atom, with the proviso that any two such heteroatoms must be separated by at least two carbon atoms, and wherein any of the alkyl moieties of said $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl- may be optionally substituted with from two to seven fluonne atoms, and wherein one of the carbon atoms of each of the alkyl moieties of said aryl-$(C_0–C_3)$alkyl- and said heteroaryl-$(C_0–C_3)$alkyl- may optionally be replaced by an oxygen, nitrogen or sulfur atom, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1–C_6)$alkyl optionally substituted with from one to seven fluonne atoms, $(C_1–C_6)$alkoxy optionally substituted with from two to seven fluorine atoms, halo (e.g., chloro, fluoro, bromo or iodo), $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, hydroxy, nitro, cyano, amino, $(C_1–C_6)$-, $[(C_1–C_6)$alkyl$]_2$amino-, $—CO_2R^4$, $—CONR^5R^6$, $—SO_2NR^7R^8$, $—C(=O)R^{13}$ and $—XC(=O)R^{13}$;

or R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or a ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents, preferably from zero to two substituents for the monocyclic rings and from zero to three substituents for the bicyclic rings, that are selected, independently, from $(C_0–C_6)$alkoxy-$(C_0–C_6)$alkyl-, wherein the total number of carbon atoms does not

exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, oxo, cyano, halo, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, hydroxy, amino, (C_1-C_6)alkylamino-, $[(C_1-C_6)alkyl]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$, and $-XC(=O)R^{13}$;

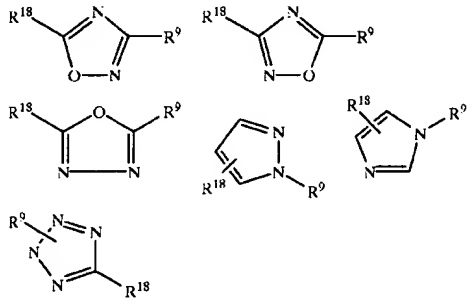
each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1-C_6)alkylene:

with the proviso that: (a) at least one of R^1, R^2 and R^3 must be the other than hydrogen, and (b) when R^2 and R^3 are hydrogen, R^1 cannot be methyl or hydrogen;

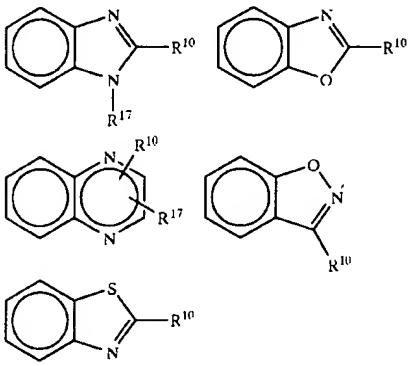
and the pharmaceutically acceptable salts of such compounds.

Examples of heteroaryl groups that each of R^2 and R^3 can be are the following: thienyl, oxazoyl, isoxazolyl, pyridyl, pyrimidyl, thiazolyl, tetrazolyl, isothiazolyl, triazolyl, imidazolyl, tetrazolyl, pyrroyl and the following groups:



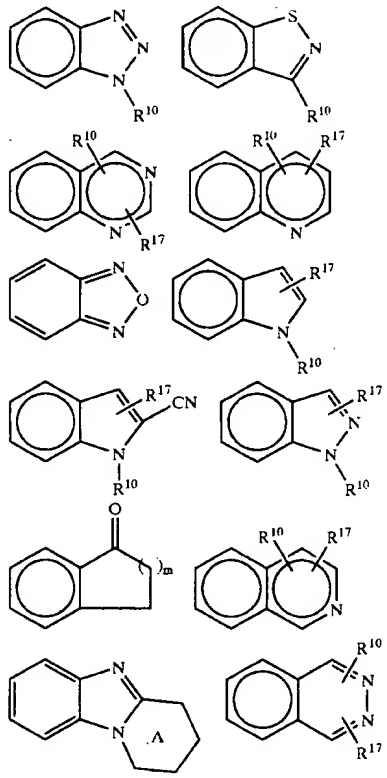
wherein one of R^9 and R^{18} is hydrogen or (C_1-C_6)alkyl, and the other is a bond to the benzo ring of formula I.

Examples of compounds of this invention are compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from (C_0-C_6)alkoxy-(C_0-C_6)alkyl- wherein the total number of carbon atoms does not exceed six and wherein any of the alkyl moieties may optionally be substituted with from one to seven fluorine atoms; nitro, cyano, halo, amino, (C_1-C_6) alkylamino-, $[(C_1-C_6)$ alkyl$]_2$amino-, $-CO_2R^4$, $-CONR^5R^6$, $-SO_2NR^7R^8$, $-C(=O)R^{13}$ $-XC(=O)R^{13}$, phenyl and monocyclic heteroaryl wherein said heteroaryl is defined as R^2 and R^3 are defined in the definition of compounds of the formula I above;

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system selected from the following:



wherein R^{10} and R^{17} are defined as above and m is zero, one or two, and wherein one of the carbon atoms of ring A can optionally be replaced with oxygen or $-N(C_1-C_6)$alkyl.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein neither R^2 nor R^3 is attached to the benzo ring of formula I via an oxygen atom.

Other embodiments of this invention relate to compounds of the formula I, and their pharmaceutically acceptable salts, wherein R^2 and R^3 do not, together with the benzo ring of formula I, form a bicyclic or tricyclic ring system.

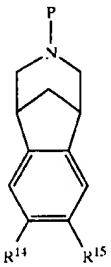
Other embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl. Further embodiments of this invention relate to compounds of the formula I wherein one or both of R^2 and R^3 are $-C(=O)R^{13}$, wherein R^{13} is (C_1-C_6)alkyl or (C_1-C_3)alkyl optionally substituted with from one to seven fluorine atoms. Other embodiments relate to compounds of the formula I wherein one of R^2 and R^3 is CF_3, fluoro, cyano or C_2F_5.

Other embodiments of this invention relate to compounds of the formula I wherein R^1 is not methyl.

Examples of specific compounds of the formula I are the following:

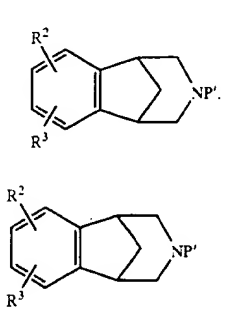
6-methyl-5,7-dioxo-6,13-diazatetracyclo[9.3 $1.0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dimethyl-6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
5,7-dioxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride:
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2 (10),3,8-triene hydrochloride;
4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene hydrochloride;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene-4-carbonitrile hydrochloride;
4-ethynyl-5-chloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7), 3,5-triene hydrochloride.
5-oxa-7-methyl-6-oxo-7,13-diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$] pentadeca-2(10),3,8-triene hydrochloride;
4-fluoro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride;
4-chloro-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride;
5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3, 5-triene-4-carbonitrile hydrochloride:
4-ethynyl-5-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene hydrochloride.
6-methyl-5-thia-5-dioxa-6,13-Diazatetracyclo[9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;
7-dimethylamino-5-thia-5-dioxa-6,13-Diazatetracyclo [9.3.1.$0^{2,10}.0^{4,8}$]pentadeca-2(10),3,8-triene hydrochloride;
6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}.0^{4,9}$] hexadeca-2(11),3,9-triene hydrochloride; and
5,8-dimethyl-6,7-dioxa-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}.0^{4,9}$]hexadeca-2(11),3,9-triene hydrochloride.

This invention also relates to compounds of the formula



wherein P is hydrogen, methyl, $COOR^{16}$ wherein R^{16} is $(C_1–C_6)$alkyl, allyl, 2,2,2-trichloroethyl or $(C_1–C_6)$alkyl; $—C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in formula I above; —C(=O)H, $—C(=O)(C_1–C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl or t-butoxycarbonyl (t-Boc); and R^{14} and R^{15} are selected, independently, from hydrogen, $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms; $—C(=O)(C_1–C_6)$alkyl, cyano, hydroxy, nitro, amino, $—O(C_1–C_6)$alkyl or halo: with the proviso that R^{14} and R^{15} can not both be hydrogen when P is hydrogen or methyl. Such compounds are useful as intermediates in the synthesis of compounds of the formula I.

The invention also relates to a compound of the formula



(I')

(I')

wherein R^2 and R^3 are defined above; and P' is $COOR^{16}$ wherein R^{16} is allyl, 2,2,2-trichloroethyl or $(C_1–C_6)$alkyl; $—C(=O)NR^5R^6$ wherein R^5 and R^6 are defined as in claim 2; —C(=O)H, $—C(=O)(C_1–C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms, preferably with from 1 to 3 fluoro or chloro atoms; benzyl, or t-butoxycarbonyl (t-Boc).

Unless otherwise indicated, the term "halo", as used herein, includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "alkyl", as used herein, includes straight, branched or cyclic, and may include straight and cyclic alkyl moieties as well as branched and cyclic moieties.

The term "alkoxy", as used herein, means "alkyl-O—", wherein "alkyl" is defined as above.

The term "alkylene, as used herein, means an alkyl radical having two available bonding sites (i.e., -alkyl-), wherein "alkyl" is defined as above.

Unless otherwise indicated, the term "one or more substituents", as used herein, refers to from one to the maximum number of substituents possible based on the number of available bonding sites.

The term "treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The compounds of formula I may have optical centers and therefore may occur in different enantiomeric configurations. The invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of formula I, as well as racemic and other mixtures thereof.

The present invention also relates to all radiolabeled forms of the compounds of the formula I. Preferred radiolabeled compounds of formula I are those wherein the radiolabels are selected from as ^3H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Such radiolabeled compounds are useful as research and diagnostic tools in metabolism pharmacokinetics studies and in binding assays in both animals and man.

The present invention also relates to a pharmaceutical composition for use in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof,

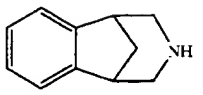
that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method of treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear, palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntingon's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

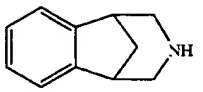
The present invention also relates to a pharmaceutical composition for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotropic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound comprising an amount of a compound of the formula



or a pharmaceutically acceptable salt thereof, that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

The present invention also relates to a method for treating a disorder or condition selected from inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic latera sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbituates, opioids or cocaine), headache, stroke, traumatic brain injury (TBI) obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula



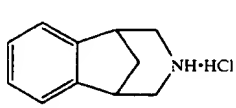
or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention also relates to the pharmaceutically acceptable acid addition salts of the compounds of formula I. Examples of pharmaceutically acceptable acid addition salts of the compounds of formula I are the salts of hydrochlonc acid, p-toluenesulfonic acid, fumaric acid, citric acid, succinic acid, salicylic acid, oxalic acid, hydrobromic acid, phosphoric acid, methanesulfonic acid, tartaric acid, malate, di-p-toluoyl tartaric acid, and mandelic acid.

DETAILED DESCRIPTION OF THE INVENTION

Except where otherwise stated, R^1 through R^{18}, m and P, and structural formula I in the reaction schemes and discussion that follow are defined as above.

Scheme 1



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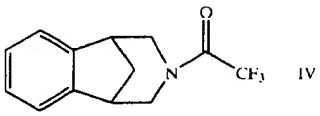

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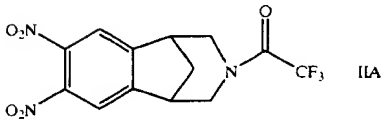
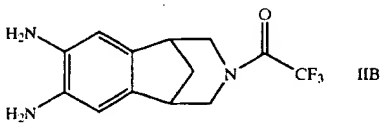
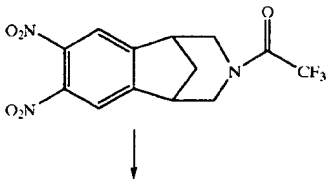


IIA



IIB

Scheme 2



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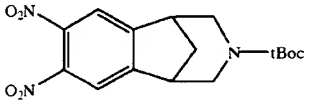

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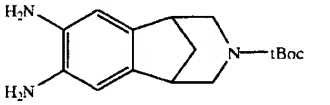

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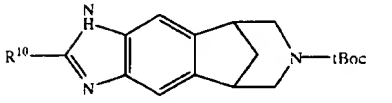

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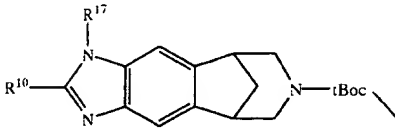

VII'

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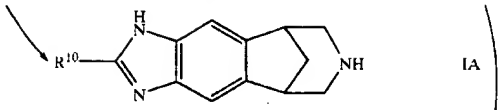
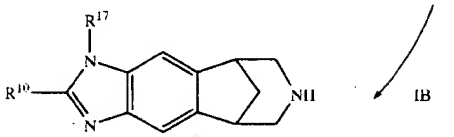
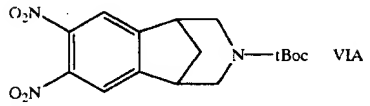


IA



IB

Scheme 3



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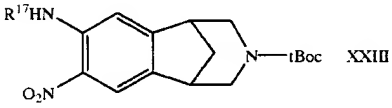

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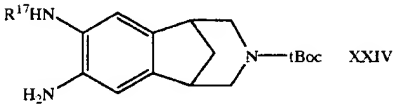

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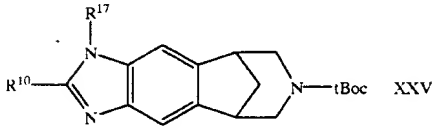

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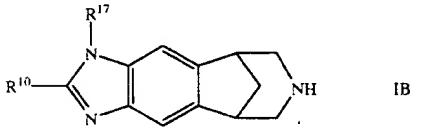

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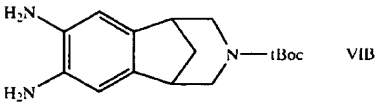
Scheme 4



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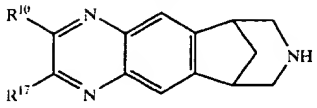

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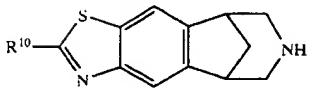
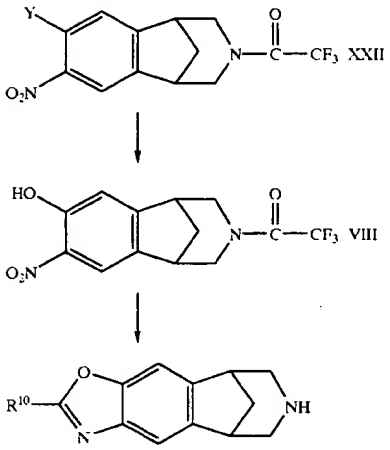


IF

Scheme 5

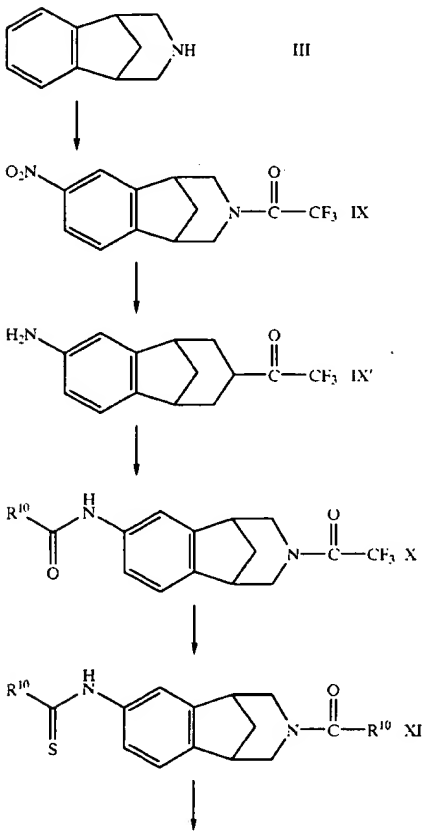


XXII

VIII

IE

Scheme 6



III

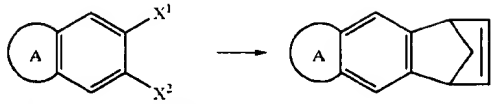
IX

IX'

X

XI

Scheme 7

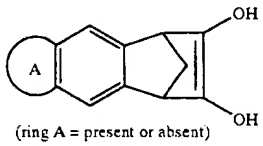


(ring A = present or absent)

XII

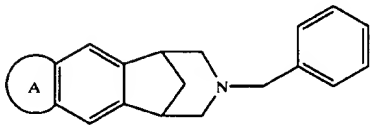
(ring A = present of absent)

XIII



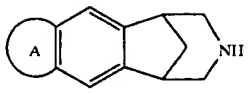
(ring A = present or absent)

XIIIA



(ring A = present or absent)

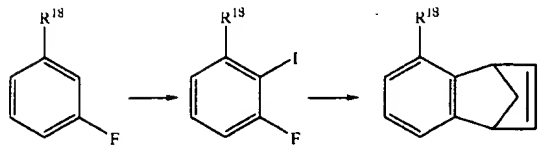
XIV



IG: (R^2 and R^3 form ring A)

III: (ring A = absent)

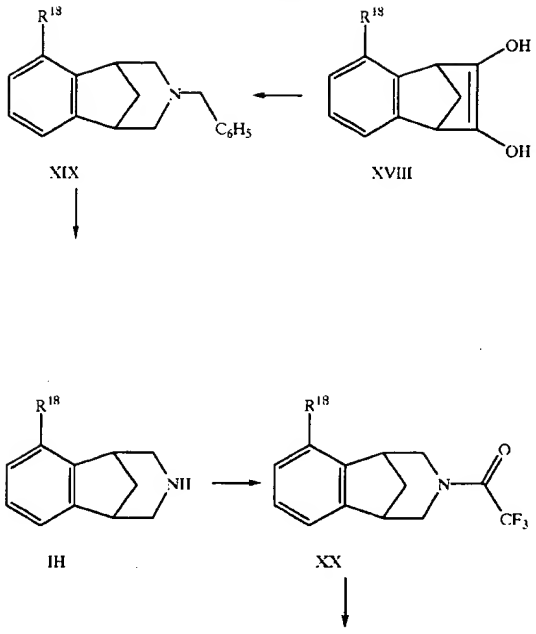
Scheme 8



XV XVI XVII

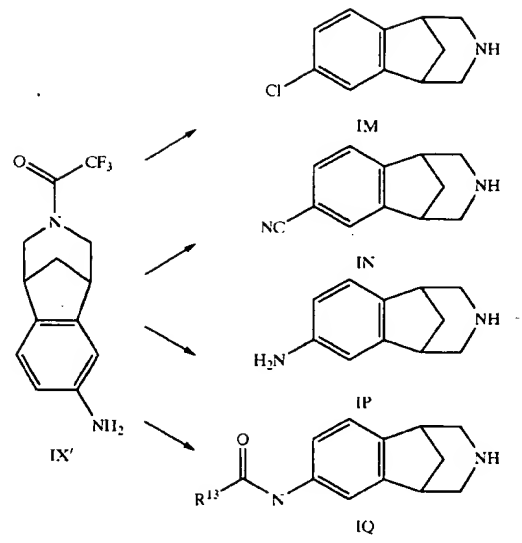
R^{18} = F or C_1-C_6)alkoxy)

-continued



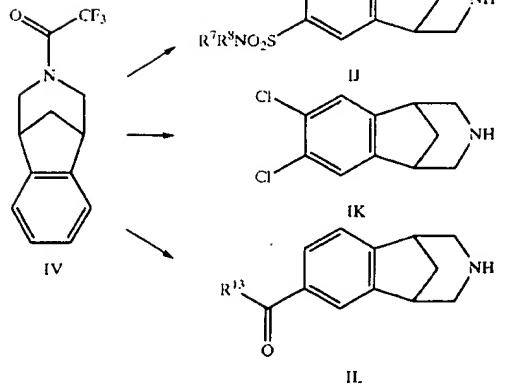
XIX XVIII IH XX XXI

Scheme 10



IX' IM IN IP IQ

Scheme 9



IV IJ IK IL

Scheme 1–10 illustrate methods of synthesizing compounds of the formula I.

Referring to Scheme 1 the starting material of formula III is reacted with trifluoroacetic anhydride, in the presence of pyridine, to form the compound of formula IV. This reaction is typically conducted in methylene chloride at a temperature from about 0° C. to about room temperature.

The compound of formula IV is then converted into the dinitro derivative of formula IIA by the following process. The compound of the formula IV is added to a mixture of 4 or more equivalents of trifluoromethanesulfonic acid (CF_3SO_2OH) and 2 to 3 equivalents of nitric acid, in a chlorinated hydrocarbon solvent such as chloroform, dichloroethane (DCE) or methylene chloride. The resulting mixture is allowed to react for about 5 to 24 hours. Both of the foregoing reactions are generally conducted at a temperature ranging from about −78° C. to about 0° C. for about 2 hours, and then allowed to warm to room temperature for the remaining time.

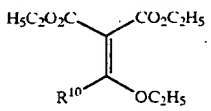
Reduction of the compound of formula IIA, using methods well known to those of skill in the art, yields the compound of formula IIB. This reduction can be accomplished, for example, using hydrogen and a palladium catalyst such as palladium hydroxide and running the reaction in methanol at about room temperature.

Referring to Scheme 2, the compound of formula IIA is converted into the corresponding compound wherein the

trifluoroacetyl protecting group is replaced by a t-Boc protecting group (VIA) by reacting it first with an alkali metal or alkaline earth metal (or ammonium) hydroxide or carbonate, and then reacting the isolated product from the foregoing reaction with di-t-butyldicarbonate. The reaction with the alkali or alkaline earth metal (or ammonium) hydroxide or carbonate is generally carried out in an aqueous alcohol, dioxane or tetrahydrofuran (THF) at a temperature from about room temperature to about 70° C., preferably at about 70° C. for about one to about 24 hours. The reaction of the isolated, unprotected amine or an acid addition salt of such amine, from the above reaction with di-t-butyldicarbonate is preferably carried out in a solvent such as THF, dioxane or methylene chloride at a temperature from about 0° C. to about room temperature. This reaction may or may not be conducted in the presence of a base. When the reactant is a salt of the amine, use of a base is preferred. The resulting compound of formula VIA can be converted into the corresponding diamino derivative of formula VIB using the procedure described above for converting the dinitro compound of formula IIA into the corresponding diamino compound of formula IIB.

The conversion of the compound of formula VIB into the desired compound of the formula VII can be accomplished by reacting the compound of formula VIB with a compound of the formula

XXIIA



wherein R^{10} is hydrogen, $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms, aryl-$(C_0–C_3)$ alkyl wherein said aryl is selected from phenyl and naphthyl, or heteroaryl-$(C_0–C_3)$alkyl wherein said heteroaryl is selected from five to seven membered aromatic rings containing from one to four heteroatoms selected from oxygen, nitrogen and sulfur, and wherein each of the foregoing aryl and heteroaryl groups may optionally be substituted with one or more substituents, preferably from zero to two substituents, independently selected from $(C_1–C_6)$alkyl optionally substituted with from one to seven fluorine atoms, $(C_1–C_6)$alkoxy optionally substituted with from one to seven fluorine atoms and cyano. The preferred solvent for this reaction is a 10:1 mixture of ethanol acetic acid. The reaction temperature can range from about 40° C. to about 100° C. It is preferably about 60° C. Other appropriate solvents include acetic acid, ethanol and isopropanol.

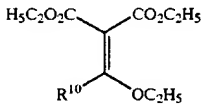
Alternate methods of preparing compounds of the formula VII the compound of formula VIB are described by Segelstein et al., *Tetrahedrón Lett.*, 1993, 34, 1897.

Removal of the t-Boc protecting group from the compound of formula VII yields corresponding compound of formula IA. The protecting group can be removed using methods well known to those of skill in the art. For example, the compound of formula VII can be treated with an anhydrous acid such as hydrochloric acid, hydrobromic acid, methanesulfonic acid, or trifluoroacetic acid, preferably hydrochloric acid in ethyl acetate, at a temperature from about 0° C. to about 100° C. preferably from about room temperature to about 70° C. for about one to 24 hours.

The compound of formula VII can be converted into the corresponding compound of formula IB by reacting it with a compound of the formula $R^{17}Z$, wherein R^{17} is defined as R^{10} is defined above, and Z is a leaving group such as a halo or sulfonate (e.g., chloro, bromo, mesylate or tosylate), in the presence of a base such as an alkali metal hydride, hydroxide or carbonate, preferably potassium hydroxide, in a polar solvent such as water, dimethylsulfoxide (DMSO), THF or DMF, preferably a mixture of DMSO and water, and then removing the protecting group as described above. The reaction with $R^{17}Z$ is generally carried out at a temperature from about room temperature to about 100° C., preferably at about 50° C., for about five hours.

Scheme 3 illustrates an alternate method of preparing compounds of the formula IB from the compound of formula VIA. This method is the preferred method of making compounds of the formula IB wherein R^{17} is a bulky group such as an aryl or heteroaryl containing group, or when R^{17} can not be attached, as illustrated in Scheme 2, by alkylation or aryl substitution methods. Referring to Scheme 3, the compound of formula VIA is reacted with the appropriate compound of formula $R^{17}NH_2$ in a polar solvent such as THF, DMF or DMSO, preferably THF, at a temperature from about room temperature to about 100° C., preferably at the reflux temperature, for about four to eighteen hours. The resulting compound of formula XXIII is then converted into the corresponding compound of the formula XXIV by reducing the nitro group to an amino group using methods well known to those of skill in the art. Such methods are referred to above for the conversion of the compounds of the formula IIA into a compound of the formula IIB in Scheme 1, and exemplified in experimental Examples 12B and 18B. Closure of the imidazole ring to form the corresponding compound of formula XXV can then be accomplished by reacting the compound of formula XXIV from the above reaction with a compound of the formula

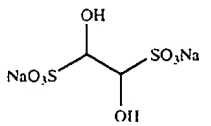
XXIIA



wherein R^{10} is defined as above, as described above for converting compounds of the formula VIB into those of the formula VII.

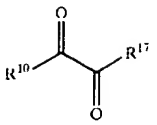
Removal of the protecting group from the compound of formula XXV yields the corresponding compound of formula IB. This can be accomplished using methods well known in the art, for example, as described above for forming compounds of the formula IA from the corresponding compounds of the formula VII.

Scheme 4 illustrates a method of preparing compounds of the formula IC, wherein R^{10} and R^{17} are as defined above. Referring to Scheme 4, the compound of formula VIB is reacted with a compound of the formula



(sodium bisulfite ethane dione addition adduct) in water or another polar solvent such as THF, DMF or DMSO, preferably a mixture of water and a water miscible solvent such as THF, for about one to four hours. The reaction temperature can range from about 40° C. to about 100° C., and is preferably at about the reflux temperature.

Alternatively, the compound of formula VIB can be reacted with a compound of the formula



(double condensation reaction) in a polar solvent such as THF, water, or acetic acid, preferably a mixture of water and THF. This reaction is typically carried out at a temperature from about 40° C. to about 100° C. preferably at the reflux temperature, for about two to four hours.

The desired quinoxoline of formula IC can then be formed by deprotecting the compound formed in either of the foregoing reactions, using the method described above for converting a compound of the formula VII into one of the formula IA.

Scheme 5 illustrates a method of preparing compounds of the formula I wherein R^2 and R^3, together with the benzo ring to which they are attached, form a benzoxazole ring system. Such a compound, wherein R^1 is hydrogen, is depicted in Scheme 5 as chemical formula IE. Referring to Scheme 5, the compound of formula XXII, wherein Y is nitro, halo, trifluoromethanesulfonate or a diazonium salt, is reacted with potassium acetate or another alkali or alkaline earth metal carboxylate in a solvent such as dimethylsulfoxide (DMSO), DMF or acetonitrile, preferably DMSO. This reaction is generally allowed to run for about 12–24 hours. Appropriate reaction temperatures range from about 70° C. to about 140° C. Approximately 100° C. is preferred.

The above reaction yields the compound of formula VIII, which can then be converted into the desired compound having formula IE by the following procedure. First, the compound of formula VIII is reduced by reaction with hydrogen and a palladium or platinum catalyst such as palladium hydroxide in methanol at a temperature from about 0° C. to about 70° C., preferably at about room temperature, to form the corresponding amino derivative. The product of this reaction is then reacted with an acid chloride of the formula $R^{10}COCl$ or an acid anhydride of the formula $(R^{10}CO)_2O$ wherein R^{10} is $(C_1–C_6)$alkyl, or a compound of the formula $R^{10}C(OC_2H_5)_3$, in an appropriate inert solvent such as decalin, chlorobenzene or xylenes. A mixture of xylenes is preferred. This reaction is typically conducted at a temperature from about 120–150° C., preferably at about 140° C. When $R^{10}COCl$ is used as a reactant, it is preferable to add a stoichiometric amount of triethylamine (TEA) or another organic tertiary amine base and a catalytic amount of pyridinium p-toluenesulfonic acid or pyridinium p-toluenesulfonate (PPTs) to the reaction mixture. When $R^{10}C(OC_2H_5)_3$ is used as a reactant, it is preferable to add a catalytic amount of PPTs to the reaction mixture.

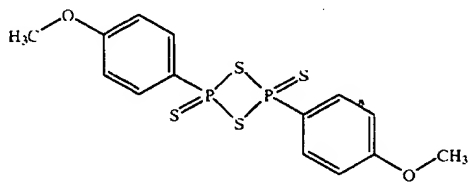
Removal of the trifluoroacetyl nitrogen protecting group yields the desired compound of the formula IE. This can be accomplished using methods well known to those of skill in the art, for example, reacting the protected compound with a lower alkanol and an aqueous alkali or alkaline earth metal (or ammonium) hydroxide or carbonate, aqueous sodium carbonate, at a temperature from about 50° C. to about 100° C., preferably at about 70° C. for about two to six hours.

Scheme 6 illustrates the preparation of compounds of the formula I wherein R^1 is hydrogen and R^2 and R^3, together with the benzo ring to which they are attached, form a benzothiazole ring system. Referring to Scheme 6, the compound of formula III is reacted with trifluoroacetic anhydride to form the corresponding compound wherein the ring nitrogen is protected by a trifluoroacetyl group, and the resulting nitrogen protected compound is then reacted with two equivalents of trifluoromethanesulfonic anhydride and one equivalent of nitric acid to form the corresponding compound of formula IX, wherein there is a single nitro substituent on the benzo ring. The reaction with trifluoroacetic acid is typically conducted in the presence of pyridine. Both of the above reactions are typically conducted in a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, at a temperature from about 0° C. to about room temperature, preferably at about room temperature.

The above transformation can also be accomplished using other nitration methods known to those skill in the art.

Reduction of the nitro group to an amine group can be accomplished as described above to provide a compound of the formula IX'.

The compound of formula IX' is then reacted with a carboxylic acid halide or anhydride of the formula $R^{10}COX$ or $(R^{10}CO)_2O$, wherein X is halo and R^{10} is hydrogen or $(C_1–C_6)$alkyl, and pyridine, TEA or another tertiary amine base, to form a compound of the formula X, which can then be converted to the desired compound having formula XI by reacting it with Lawesson's reagent, which is depicted below



The reaction with $R^{10}COX$, wherein X is halo, or $(R^{10}CO)_2O$ is generally carried out at a temperature from about 0° C. to about room temperature, preferably at about room temperature. The reaction with Lawesson's reagent is generally carried out in a reaction inert solvent such as benzene or toluene, preferably toluene, at a temperature from about room temperature to about the reflux temperature of the reaction mixture, preferably at about the reflux temperature.

Closure to the benzothiazole ring and nitrogen deprotection to form the desired compound of formula IF can be accomplished by reacting the compound of formula XI with potassium ferricyanide and sodium hydroxide in a mixture of water and methanol ($NaOH/H_2O/CH_3OH$), at a temperature from about 50° C. to about 70° C., preferably at about 60° C. for about 1.5 hours.

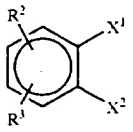
Scheme 7 illustrates a method of preparing the compound of formula III, which is used as the starting material for the process of Scheme 1, or a compound of the formula IG, wherein R^2 and R^3 form a ring (labeled "A" in the Scheme), as defined above in the definition of compounds of the formula I. Referring to Scheme 7, the compound of formula XII, wherein X^1 and X^2 are selected, independently, from chloro, fluoro, bromo and iodo, but where at least one of X^1 and X^2 is Br- or I-, reacted with cyclopentadiene, in the presence of magnesium metal, in a THF, dioxane or other ethereal solvent, at a temperature from about 40° C. to about 100° C., preferably at about the reflux temperature, to form a compound of the formula XIII. Reaction of the resulting compound of formula XIII with N-methylmorpholine-N-oxide (NMO) and osmium tetroxide in acetone at about room temperature yields the corresponding compound of the formula XIIIA.

The compound having formula XIIIA is then converted into the corresponding compound of formula XIV using the following procedure. First, the compound of formula XIIIA is reacted with sodium periodate in a mixture of a chlorinated hydrocarbon, preferably dichloroethane (DCE), and water, or with lead tetraacetate in a chlorinated hydrocarbon solvent, at a temperature from about 0° C. to about room temperature, to generate a dialdehyde or glycal intermediate. The product of this reaction is then reacted with benzylamine and sodium triacetoxyborohydride in a chlorinated hydrocarbon solvent at a temperature from about 0° C. to about room temperature, preferably at about room temperature, to form the desired compound of formula XIV. Removal of the benzyl group from the compound of formula XIV yields the compound of formula III (when ring A is absent) or IG, (when ring A is present). This can be accomplished using methods well known to those of skill in the art, for example, optionally reacting the free base with one equivalent of acid, e.g., hydrochloric acid, (to form the corresponding acid addition salt), followed by hydrogen and palladium hydroxide in methanol at about room temperature.

In the reductive animation step described above and throughout this document, alternatives to benzyl amine, such as ammonia, hydroxylamine, alkoxy amines, methyl amine, allyl amine, and substituted benzyl amines (e.g., diphenylmethyl amine and 2- and 4-alkoxy substituted benzyl amines) can also be used. They can be used as free bases, or as their salts, preferably their acetate salts, and can be subsequently removed by methods described for each by T. W. Greene and G. M. Wuts, "Protective Groups in Organic Synthesis", 1991, John Wiley & Sons, New York, N.Y.

The procedure of Scheme 7 can also be used to prepare compounds of the formula I wherein R^2 and R^3 do not form a ring and are not both hydrogen, by replacing the starting material of formula XII with the appropriate compound having the formula

XII'



Scheme 8, 9 and 10 illustrate methods of preparing compounds of the formula I wherein R^1 is hydrogen: and R^2 and R^3 represent a variety of different substituents, as defined above, but do not form a ring.

Scheme 8 illustrates a variation of the process shown in Scheme 7, which can be used to make a compound identical to that of formula III except that the benzo ring is substituted with a fluoro group or an alkoxy group (R^{18} in Scheme 8). This compound is depicted in Scheme 8 as chemical structure 1H. Referring to Scheme 8, where, for example, R^{18} is F, 1,3-difluorobenzene is reacted with a strong base such as an alkali metal dialkylamine or an alkali metal alkyl (or aryl) in an ethereal solvent such as ethyl ether or THF, at a temperature below −50° C. followed by quenching with iodine or N-iodosuccinamide, to form 1,3-difluoro-2-iodobenzene. The compound 1,3-difluoro-2-iodobenzene (structural formula XVI in Scheme 8) is then converted into the compound of formula IH by a series of reactions (represented in Scheme 8 as XVI→XVII→XVIII→XIX→IH) that are analogous to the series of reactions described above and illustrated in Scheme 7 for converting compounds of the formula XIII into those of the formula IG or III. Conversion of the compound of formula XVI into the compound of formula XVII can also be accomplished by treating a mixture of the compound of formula XVI and cyclopentadiene with an alkyl lithium reagent, preferably n-butyl lithium, in an inert hydrocarbon solvent such as petroleum ether or methyl cyclohexane, at a temperature from about −20° C. to about room temperature, preferably at about 0° C.

The compound of formula IH can then be converted into the corresponding nitrogen protected derivative of formula XX, using the methods described above for synthesizing the compound of formula IV in Scheme 1. Nitration of the compound of formula XX using the method described above for preparing the compound of formula IX in Scheme 6, yields the compound of formula XXI wherein the benzo ring is substituted with both a fluoro and nitro group or an alkoxy group and nitro group. The compound of formula XXI can be used to make a variety of compounds of the formula I wherein one of R^2 and R^3 is fluoro, using methods that are well known to those of skill in the art, for example, by first converting the nitro group to an amino group, converting the amino group to a variety of other substituents, as illustrated in Scheme 10, and then removing the nitrogen protecting group.

The compound of formula XXI acts as a regioisomeric functional equivalent of the compounds having formulas IIA, VIA and XXII, in that the fluorine atom of formula XXI reacts similarly to the nitro and Y groups of formula IIA, VIA, and XXII, and thus can be subjected to the same series of reactions as those described above for the latter three compounds, providing an alternate means for preparing the products of such reactions. Similarly, the alkoxy group of formula XXI (R^{18}=alkoxy) may be converted into a hydroxyl group before or after introduction of the nitro group, and then converted to isomeric products as described above. Also, the trifluoromethanesulfonate salt of such hydroxy derivative can act as a Y-group as described.

Preparation of compounds of formula I where R^2=—O(C_1–C_6)alkyl, (C_1–C_6) alkyl or aryl wherein aryl is defined as above in the definition of formula I, and R^3 is H or one of the other substituents described above in the definition of formula I, can be prepared as described above and illustrated in Scheme 8 by replacing one of the fluorine atoms of the compound of formula XV with —O—(C_1–C_6)alkyl, (C_1–C_6)alkyl or aryl, respectively.

Scheme 9 illustrates methods of preparing compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is $R^7R^8NO_2S$—: (b) R^1 and R^2 are both chloro: and (c) R^1 is hydrogen and R^2 is $R^{13}C(=O)$—. These compounds are referred to in Scheme 9, respectively, as compounds of formulas IJ, IK and IL.

Referring to Scheme 9, compounds of the formula IJ can be prepared by reacting the compound of formula IV with two or more equivalents of a halosulfonic acid, preferably chlorosulfonic acid, at a temperature from about 0° C. to about room temperature. Reaction of the chlorosulfonic acid derivative so formed with an amine having the formula R^7R^8NH, wherein R^7 and R^8 are defined as above, followed by removal of the nitrogen protecting group, yields the desired compound having formula IJ.

Compounds of the formula IK can be prepared by reacting the compound of formula IV with iodine trichloride in a chlorinated hydrocarbon solvent, followed by removal of the nitrogen protecting group. The reaction with iodine trichloride is typically carried out at a temperature from about 0° C. to about room temperature, and is preferably carried out at about room temperature. In a similar fashion, the analo-

gous mono- or dibrominated or mono- or diiododinated compounds can be prepared by reacting the compound of IV with N-iodosuccinimide or N-bromosuccinimide in a trifluoromethanesulfonic acid solvent, followed by removal of the nitrogen protecting group as described above.

Reaction of the compound of IV with an acid halide of the formula $R^{13}COCl$ or an acid anhydride of the formula $(R^{13}CO)_2O$, with or without a reaction inert solvent such as a chlorinated hydrocarbon solvent, preferably methylene chloride, in the presence of Lewis acid such as aluminum chloride, at a temperature from about 0° C. to about 100° C., followed by nitrogen deprotection, yields the compound of formula IL. The reaction with the acid halide or anhydride can be carried out using other known Lewis acids or other Friedel-Crafts, acylation methods that are known in the art.

The reactions described herein in which NO_2, $—SO_2NR^7R^8$, $—COR^{13}$, I, Br or Cl are introduced on the compound of formula IV, as depicted in Scheme 9 and described above, can be performed on any analogous compound wherein R^2 is hydrogen, $(C_1–C_6)$alkyl, halo, $(C_1–C_6)$ alkoxy or $—NHCONR^7R^8$, producing compounds of the formula I wherein R^2 and R^3 are defined as in the definition of compounds of the formula I above.

Compounds that are identical to those of the formula IL, but which retain the nitrogen protecting group, can be converted into the corresponding O-acyl substituted compounds, i.e., those wherein the $—C(=O)R^{13}$ group of formula IL is replaced with a $—O—C(=O)R^{13}$ group, using Baeyer-Villiger processes well known to those skilled in the art. The resulting compounds can be partially hydrolyzed, as described in Example 35, to yield the corresponding hydroxy substituted compounds, and then alkylated to form the corresponding alkoxy substituted compounds. Also, as described in Example 36, such O-acyl substituted compounds can be used to prepare variably substituted benzisoxazoles.

Scheme 10 illustrates methods of making compounds of the formula I wherein: (a) R^1 is hydrogen and R^2 is chloro; (b) R^1 is hydrogen and R^2 is cyano; (c) R^1 is hydrogen and R^2 is amino; and (d) R^1 is hydrogen and R^2 is $R^{13}C(=O)N(H)—$. These compounds are referred to in Scheme 10, respectively, as compounds of the formula IM, IN, IP and IQ.

Compounds of formula IM can be prepared from compounds of the formula IX' by generation of a diazonium salt with, for instance, an alkali metal nitrite and strong mineral acid (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid) in water, followed by reaction with a copper halide salt, such as copper (I) chloride. Nitrogen deprotection by the methods described above yields the desired compound of formula IM. Alternative methods for the generation of diazonium salts, as known and practiced by those of skill in the art, can also be used. The foregoing reaction is generally carried out by temperatures ranging from about 0° C. to about 60° C., preferably about 60° C. for about 15 minutes to one hour.

Reaction of the diazodium salt, prepared as described above, with potassium iodide in an aqueous medium provides the analogous iodide derivative. This reaction is generally carried out at a temperature from about 0° C. to about room temperature, preferably at about room temperature. The resulting compound, or its analogous N-tert-butylcarbonate protected form, can be used to prepare the corresponding cyano derivative by reaction with copper (I) cyanide and sodium cyanide in DMF, N,N-dimethylpropylurea (DMPU) or DMSO, preferably DMF, at a temperature from about 50° C. to about 180° C., preferably about 150° C. Nitrogen deprotection as described above provides the desired compound of formula IM.

The above described iodide derivative can also be used to access a variety of other substituents such as aryl, acetylene and vinyl substituents, as well as the corresponding carbonyl esters and amides, by palladium and nickel catalyzed processes known to those of skill in the art, such as Heck, Suzuki and Stille couplings and Heck carbonylations.

Nitrogen deprotection of the compound of formula IX' provides the compound of the formula IP.

The compound of formula IX' can be reacted with a acyl group having the formula $R^{13}COCl$ or $(R^{13}CO)_2O$ using the methods described above, followed by nitrogen deprotection to provide compounds of the formula IQ. In a similar fashion. treatment of the protected amine with a compound having the formula $R^{13}SO_2X$, when X is chloro or bromo, followed by nitrogen deprotection, provides the corresponding sulfonamide derivative.

Other suitable amine protecting groups that can be used, alternatively, in the procedures described throughout this document include $—COCF_3$, $—COCCl_3$, $—COOCH_2CCl_3$, $—COO(C_1–C_6)$alkyl and $—COOCH_2C_6H_5$. These groups are stable under the conditions described herein, and may be removed by methods described for each in Greene's "Protective Groups in Organic Chemistry", referred to above.

In each of the reactions discussed above, or illustrated in Schemes 1–10, above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, with ambient pressure, i.e., about 1 atmosphere, being preferred as a matter of convenience.

The compounds of the formula I and their pharmaceutically acceptable salts (hereafter "the active compounds") can be administered via either the oral, transdermal (e.g., through the use of a patch), intranasal, sublingual, rectal, parenteral or topical routes. Transdermal and oral administration are preferred. These compounds are, most desirably, administered in dosages ranging from about 0.25 mg up to about 1500 mg per day, preferably from about 0.25 to about 300 mg per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 0.01 mg to about 10 mg per kg of body weight per day is most desirably employed. Variations may nevertheless occur depending upon the weight and condition of the persons being treated and their individual responses to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval during which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compounds can be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the several routes previously indicated. More particularly, the active compounds can be administered in a wide variety of different dosage forms, e.g., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, transdermal patches, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic

solvents. In addition, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc can be used for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar] as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration the active ingredient may be combined with various sweetening or flavoring agents, coloring matter and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

For parenteral administration. a solution of an active compound in either sesame or peanut oil or in aqueous propylene glycol can be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8), if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

It is also possible to administer the active compounds topically and this can be done by way of creams, a patch, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

Biological Assay

The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in *The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm.*, 29, 448–54, (1986)) and Anderson, D. J. and Arnenc, S. P. (in *Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm.*, 253, 261–67 (1994)).

Procedure

Male Sprague-Dawley rats (200–300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.–7 p.m. light period). They received standard Purina Rat Chow and water ad libitum.

The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (*Molec Pharmacol*, 29, 448–454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0° in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000×g; 0 to 4° C. The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000×g; 0 to 4° C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0 g/100 mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 74 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50 μL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 μL of [^{3}H]-nicotine in assay buffer followed by 750 μL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 μM The vehicle consisted of deionized water containing 30 μL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4° C. in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40–50% efficiency All determinations were in triplicate.

Calculations

Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

$$\text{Specific binding}=(C)=(A)-(B).$$

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E)=(D)-(B).

$$\% \text{ Inhibiton}=(1-((E)/(C)) \text{ times } 100.$$

The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10 μM.

The following experimental examples illustrate, but do not limit the scope of, this invention.

EXAMPLE 1

10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE

A) 1,4-Dihydro-1,4-methano-naphthalene

(Based wholly or in part on a) Wittig, G.; Knauss, E. *Chem. Ber.* 1958, 91, 895. b) Muir, D. J.; Stothers, J. B. *Can. J. Chem.* 1993, 71, 1290.)

Magnesium turnings (36.5 g, 1.5 M) were stirred in anhydrous THF (250 mL) in a dried 2 L 3 neck round bottom flask equipped with a 250 mL non-equalizing addition funnel with a nitrogen (N_2) flow adapter, mechanical stirrer

and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2-Fluorobromobenzene (2 g) was added followed by 1 mL of 3N ethylmagnesium bromide (EtMgBr in THF). The addition funnel was charged with a mixture of cyclopentadiene (94.4 g, 1.43 M. Prepared by the method described in: *Org. Syn.* Col. Vol. V, 414–418) and bromofluorobenzene (250 g, 1.43 M) which was maintained at 0° C. in a separate flask by an ice bath, and transferred to the addition funnel via cannula. Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation), the heating mantle was removed and the contents of the addition funnel was added dropwise at such rate as to maintain reflux (1.5 hours) The heating mantle was re-applied and a reflux maintained for 1.5 hours. (TLC 100% hexanes R_f0.67).

The reaction was cooled to room temperature and quenched with H_2O (500 mL) and carefully with 1N HCl (200 mL, produces H_2 evolution from unconsumed Mg). To this ~50 mL concentrated HCl was added to dissolve solids. Total addition/quench time ~1 hour. Saturated aqueous sodium chloride (NaCl) solution (300 mL) was added and product hexanes extracted until no potassium permanganate ($KMnO_4$) active product is removed, (4×~250 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (250 mL), sodium bicarbonate Na_2SO_4 dried and concentrated to an oil (~200 g). The product was distilled at 78–83° C. @ 15 mm (131 g, 64%). (An alternative workup is described on p.419 Fieser and Fieser, Vol. I, Reagents for Organic Synthesis, Wiley, N.Y., N.Y.; 1967).

B) 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol

(Except for the workup method and the quantity of OsO_4 used, based on VanRheenen, V.; Cha. D. Y.; Hartley, W. M. *Org. Syn.* 1988, 6, 342.)

In a 2 L 3 neck round bottom flask equipped with a N_2 flow adapter, mechanical stirrer was placed 1,4-dihydro-1,4-methano-naphthalene (79.5 g, 560 mmol) stirred in acetone (800 mL) and H_2O (100 mL) and N-methyl morpholine N-oxide (67.5 g, 576 mmol). To this was added osmium tetroxide (OsO_4) (15 mL of a 15 mol % t-BuOH solution, 1.48 mmol. 0.26 mol %) and the mixture was stirred vigorously. After 60 hours, the reaction was filtered, and the white product rinsed with acetone and air dried (60.9 g). The mother liquor was concentrated to an oily solid: acetone trituration, filtration and acetone rinse provided (27.4 g, total 88.3 g, 89%). (TLC 50% EtOAc/hexanes R_f~0.5). mp 176–177.5° C.

C) 10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(Based on Abdel-Magid, A. F.; Carson, K. G.; Harris. B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* 1996, 61, 3849; and Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* 1979. 22, 455.)

1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round bottom flask under nitrogen with cool water bath (~10° C.). To this sodium periodate ($NaIO_4$) (51 g, 239 mmol) and triethylbenzyl ammonium chloride (Et_3BnNCl) (50 mg) were added. The resulting mixture was stirred for 1 hour (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with DCE (200 mL). The organic layer was washed with H_2O (4×200 mL, or until no reaction to starch iodide is observed in the aqueous wash) then dried through a cotton plug. To this was added benzyl amine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 minutes then immediately transferred into the sodium triacetoxyborohydride $NaHB(OAc)_3$/DCE (see below) over 10 minutes.

In a separate 2 L round botton flask flask under nitrogen was magnetically stirred $NaHB(OAc)_3$ (154 g, 0.727 mmol) in DCE (800 mL) at 0° C. (ice bath). To this was added the above mixture over 10 minutes, without delay after the dialdehyde and amine were mixed. The resulting orange mixture was allowed to warm to room temperature and stirred for 30–60 minutes.

The reaction was quenched by addition of saturated sodium carbonate (Na_2CO_3) solution (~300 mL) carefully at first and the mixture was stirred for 1 hour (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×300 mL). The organic layer was washed with saturated aqueous NaCl solution (200 mL), dried through a cotton plug, then evaporated to a red oil. This was dissolved in a minimum of Et_2O and filtered through a Silica pad (3×4 inch) eluting with 15% ethyl acetate (EtOAc)/hexanes +1% of 37% aqueous ammonium hydroxide (NH_4OH) solution to remove baseline red color. Concentration affords a light yellow oil (48.5 g, 194.8 mmol, 85.7%). (TLC 10% EtOAC/hexanes R_f0.75). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.16 (m, 7H), 6.89 (m, 2H), 3.48 (m, 2H), 3.08 (m, 2H), 2.80 (d, J=9.5 Hz, 2H), 2.42 (d, J=9.5 Hz, 2H), 2.27 (m, 1H), 1.67 (d, J=10.0 Hz, 1H). APCI MS m/e 250.3 [(M+1)$^+$].

D) 10-Aza-tricyclo[6.3.1.$0^{2,7}$]-dodeca-2(7),3,5-triene (For an alternative synthesis, see; Mazzocchi, P. H.; Stahly, B. C. *J. Med. Chem.* 1979, 22, 455.)

10-Benzyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3N HCl EtOAc (1.03 eq.) slowly with cooling (ice bath). The resulting precipitate was filtered and rinsed with EtOAc. The solids were dissolved in MeOH (250 mL) in a parr bottle. To this was added $Pd(OH)_2$ (7 g of 20% wt/C) and the mixture was shaken under 50–40 psi of H_2 for 24 hours or until done by TLC. The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotroped with methanol (MeOH) (3×) then triturated with acetone, treated with ethyl ether (Et_2O) to precipitate product and filtered. Concentration of the mother liquors and a second treatment provided an off white solid (48.95 g, 251 mmol, 88%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 4H), 2.97 (m, 4H), 2.68 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 1.95 (d, J=11.0 Hz, 1H) APCI MS m/e 160.2 [(M+1)$^+$].

EXAMPLE 2

4-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 6-Fluoro-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* 1976, 98, 753–761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* 1977, 99, 3723–3733.)

Magnesium turnings (0.66 g, 27.2 mmol) were stirred in anhydrous THF (10 mL) in a flame dried 75 mL 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter, magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,5-Difluorobromobenzene (0.1 g) was added followed by of 3N EtMgBr in THF (0.1 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (1.71 g, 25.9 mmol) and 2,5-difluorobromobenzene (5.0 g, 25.9 mmol). Small portions (~0.2 mL) of the intimate mixture

were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of the contents of the addition funnel. The reaction was then maintained at reflux for 1 hour.

The reaction was cooled to room temperature and quenched with H_2O (20 mL) followed by aqueous 1N HCl solution (20 mL) to dissolve the solids. Saturated aqueous NaCl solution (30 mL) was added and product was extracted with hexanes (4×25 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil. Chromatography on Silica gel eluting with hexanes provided an oil (780 mg, 19%). (TLC hexanes R_f0.38). ^1H NMR (400 MHz, $CDCl_3$) δ7.10 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.80 (br s, 1H), 6.78 (br s, 1H), 6.59 (m, 1H), 3.87 (br s, 2H) 2.32 (d. J=7.0 Hz, 1H), 2.25 (d, J=7.0 Hz. 1H).

B) 6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

6-Fluoro-1,4-dihydro-1,4-methano-naphthalene (680 mg, 4.22 mmol) and N-methyl morpholine N-oxide (599 mg, 4.43 mmol) were stirred in acetone (50 mL) and H_2O (5 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5% wt. solution in t-BuOH, 0.02 mmol). After 72 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for 1 hour. The florisil was filtered and the filtrate concentrated to produce a crystalline product which was triturated with acetone and filtered (524 mg, 64%) ^1H NMR (400 MHz. $CDCl_3$) δ7.10(dd, J=8.0,5.0 Hz, 1H), 6.90 (dd, J=8.0,2.3 Hz, 1H), 6.75 (ddd, J=8.0,8.0,2.3 Hz, 1H), 3.79 (s, 2H), 3.18 (d, J=1.5 Hz, 2H), 2.22 (d, J=10.0 Hz, 1H), 1.92 (dd, J=10.0,1.5 Hz, 1H). GCMS m/e 194 (M^+).

C) 10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

6-Fluoro-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (524 mg, 2.68 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (15 mL) and H_2O (45 mL) then treated with sodium periodate (0.603 mg, 2.82 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2×20 mL). The combined organic layer was washed with H_2O (4×20 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (20 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (0.308 mL, 2.82 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0° C.) mixture of $NaHB(OAc)_3$ (1.82 g, 8.58 mmol) in DCE (50 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (520 mg, 80%). (TLC 2% acetone/CH_2Cl_2 R_f 0.40). ^1H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 1H), 6.88 (m, 2H), 3.48 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.41 (m, 2H), 2.27 (m, 1H), 1.69 (d, J=10.5 Hz, 1H).

D) 4-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (390 mg, 1.461 mmol), ammonium formate (3.04 g, 48.2 mmol) and 10% $Pd(OH)_2/C$ (30 mg) were combined in MeOH (50 mL) and brought to reflux under N_2 for 1.5 hours. Ammonium formate (1.0 g) was added and reflux continued for 0.5 hour. The reaction mixture was filtered through a Celite pad which was rinsed with MeOH. The filtrate was concentrated. The residues were treated with saturated aqueous Na_2CO_3 solution (30 mL) and product extracted with methylene chloride (CH_2Cl_2) (3×25 mL). The organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. The residue was treated with 2N HCl MeOH (5 mL) and concentrated then taken up in minimum of MeOH and saturated with Et_2O. After stirring 18 h. the white crystals were collected by filtration (86 mg, 28%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.27), (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ7.06 (m, 1H), 6.83 (m, 2H), 2.89 (m, 4H), 2.61 (dd, J=12.0 Hz, 2H), 2.37 (m, 1H), 1.87 (d, J=11.5 Hz, 1H). APCI MS m/e 178.2 [(M+1)$^+$]. (HCl salt) mp 260–262° C.

EXAMPLE 3

4-METHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-methylbromobenzene. (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ7.04 (d, J=7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d, J=7.5 Hz, 1H), 2.98–2.90 (m, 4H), 2.63 (m, 2H), 2.35 (m, 1H), 2.32 (s, 3H), 1.87 (d, J=11.5 Hz, 1H). APCI MS m/e 174.2 [(M+1)$^+$]. (HCl salt) mp 254–255° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.82; N, 5.15.

EXAMPLE 4

4-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L., Paradkar. V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall. D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* 1983, 48, 2321–2327. Grunewald, G. L.; Markovich. K. M.; Sall. D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-5-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ7.71 (s, 1H), 7.64 (d, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 1H), 3.46 (m, 4H), 3.21 (d, J=12.5 Hz, 2H), 2.41 (m, 1H), 2.16 (d, J=11.5 Hz, 1H) APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 244–246° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$; C, 53.44; H, 5.11; N, 5.19. Found C. 53.77; H, 4.82; N, 5.18.

EXAMPLE 5

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (Grunewald. G. L.; Markovich, K. M.; Sall. D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^1H NMR (400 MHz, CD_3OD) δ7.65 (s, 2H), 7.52 (m, 1H), 3.65 (br s, 1H), 3.49–3.43 (m, 3H), 3.20 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=1.5 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 275–277° C.

EXAMPLE 6

3-FLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 2,6-Difluoroiodobenzene (Roe, A. M.; Burton, R. A.; Willey, G. L.; Baines. M. W.; Rasmussen, A. C. *J. Med. Chem.* 1968, 11, 814–819. Tamborski, C.; Soloski, E. J. *Org. Chem.* 1966, 31, 746–749. Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. J. *J. Med. Chem.* 1986, 29, 1972–1982.) 1,3-Difluorobenzene (57.05 g, 0.5 M) in THF (75 mL) was added to a −78° C. stirred solution of n-butyllithium (n-BuLi) (200 mL, 2.5 M/hexanes, 0.5 M) and THF (500 mL) under N_2. By controlling the addition rate the internal temperature was maintained below −70° C. The total addition time was ~½ hour. The resulting slurry was stirred an additional ½ hour, then the dispersion was treated with a solution of iodine (126.9 g, 0.5 M) in THF (300 mL) at a rate that maintained an internal temperature below −70° C. After complete addition the mixture was allowed to warm to room temperature, and was treated with H_2O (100 mL) and 10% aqueous $Na_2S_2O_3$ solution (100 mL) and stirred. The layers were separated and the aqueous layer extracted with hexanes (2×250 mL). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL), H_2O (100 mL). saturated aqueous NaCl solution (100 mL), dried (Na_2SO_4) filtered and concentrated to give a yellow oil (106.5 g). Distillation at ~1–5 mm at −80° C. provided a light yellow oil (89.5 g, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ7.30 (m, 1H), 6.87 (m, 2H) GCMS m/e 240 (M^+).

B) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene

A solution of 2,6-difluoroiodobenzene (5.0 g, 20.8 mmol) and cyclopentadiene (2.07 g, 31.3 mmol) was stirred at 0° C. in P, ether (70 mL, 40–60° C.) under N_2 and treated with n-BuLi (8.74 mL, 2.5M in hexanes, 21.8 mmol) dropwise over 10 minutes. The reaction was quenched after 15 minutes by addition of aqueous 1N HCl solution and the product was extracted with hexanes (3×50 mL). The combined organic layer was washed with H_2O (50 mL), saturated aqueous NaCl solution (50 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography on Silica gel provided product as an oil (1.5 g, 45%) (TLC hexanes R_f0.55). ^1H NMR (400 Mhz, $CDCl_3$) δ7.08 (ddd, J=7.0,1.0,0.8 Hz, 1H), 6.96 (ddd, J=8.5,8.3,7.0 Hz, 1H), 6.86 (br s, 2H), 6.72 (ddd, J=8.5,8.3, 0.8 Hz, 1H), 4.25 (br s, 1H), 3.98 (br s, 1H), 2.36 (ddd, J=7.2,1.7,1.7 Hz, 1H), 2.30 (ddd, J=7.2,1.7,1.5 Hz, 1H), GCMS m/e 160 (M^+).

C) 3-Fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

The title compound was prepared by the methods described in Example 2B,C,D starting with 5-fluoro-1,4-dihydro-1,4-methano-naphthalene. ^1H NMR (400 Mhz, CD_3OD) δ7.36 (ddd, J=8.3,7.3,5.0 Hz, 1H), 7.21 (d, J=7.3 Hz, 1H), 7.07 (t, J=8.3 Hz, 1H), 3.62 (br s, 1H), 3.42–3.30 (m, 3H), 3.21 (m, 2H), 2.38 (m, 1H), 2.12 (d, J=11.5 Hz, 1H). APCI MS m/e 178.4[(M+1)$^+$]. mp 269–271° C.

EXAMPLE 7

4-NITRO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride salt (12.4 g, 63.9 mmol) was stirred in CH_2Cl_2 (200 mL). This was cooled (ice bath) and treated with pyridine (12.65 g 160 mmol) followed by trifluoroacetic anhydride (TFAA) (16.8 g, 11.3 mL, 80 mmol) from an addition funnel over 10 minutes. After ~3 hours, the solution was poured into 0.5N aqueous HCl (200 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layer was washed with 0.5N aqueous HCl (50 mL), H_2O (2×50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL)). This solution was dried through a cotton plug, then diluted with ~3% EtOAc and filtered through a 2 inch Silica pad eluted with ~3% EtOAc/CH_2Cl_2. Concentration afforded a clear oil which crystallized to give white needles (15.35 g, 60.2 mmol, 94%). (TLC 30% EtOAc/hexanes R_f0.53). ^1H NMR (400 MHz, $CDCl_3$) δ7.18 (m, 4H), 4.29 (br d, J=12.6 Hz, 1H), 3.84 (br d, J=12.6 Hz, 1H), 3.51 (dd, J=12.6,1.5 Hz, 1H), 3.21 (br s. 1H), 3.10 (br s, 1H), 3.10 (br d, J=12.6 Hz, 1H), 2.37 (m, 1H), 1.92 (d, J=10.8 Hz, 1H). GCMS m/e 255 (M^+). mp 67–68° C.

B) 1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (Based on the method described by Coon, C. L., Blucher. W. G.; Hill, M. E. *J. Org. Chem.* 1973, 25, 4243.)

To a solution of trifluoromethanesulfonic acid (2.4 ml, 13.7 mmol) in CH_2Cl_2 (10 ml) stirred at 0° C. was slowly added nitric acid (0.58 ml, 27.4 mmol) generating a white precipitate. After 10 minutes the resulting mixture was cooled to −78° C. and treated with 1-(10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-yl)-2,2,2-triflouro-ethane (3.5 g, 13,7 mmol) in CH_2Cl_2 (15 ml) dropwise from an addition funnel over 5 minutes. The reaction was stirred at −78° C. for 30 minutes then warmed to 0° C. for 1 hour. The reaction mixture was poured into a vigorously stirred ice (100 g) The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×30 ml). The organic layer was combined and washed with H_2O (3×30 ml). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (20 mL) and H_2O (20 mL) then dried through a cotton plug and concentrated to give an orange oil that solidified on standing (4.2 g). Chromatography yielded pure product as a crystalline solid (3.2 g, 78%). (TLC 30% EtOAc/hexanes R_f0.23). ^1H NMR (400 MHz, $CDCl_3$) δ8.12 (br d, J=8.0 Hz, 1H), 8.08 (br s, 1H), 7.37 (br d, J=8.0 Hz, 1H), 4.38 (br d, J=12.6 Hz, 1H), 3.94 (br d, J=12.6 Hz, 1H), 3.59 (br d, J=12.6 Hz, 1H), 3.43–3.35 (m, 2H), 3.18 (br d, J=12.6 Hz, 1H), 2.48 (m, 1H), 2.07 (d, J=10.8 Hz, 1H). GCMS m/e 300 (M^+).

C) 4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4-Nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (182 mg, 0.61 mmol) was stirred with Na_2CO_3 (160 mg, 1.21 mmol) in MeOH (3 mL) and H_2O (1 mL) at 70° C. for 18 hours. The mixture was concentrated, water was added and the product was extracted with CH_2Cl_2. The organic layer was extracted with 1N aqueous HCl (3×20 mL) and the acidic layer washed with CH_2Cl_2 (2×20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3(s) and product was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried through a cotton plug and concentrated to an oil. This was dissolved in MeOH and treated with 1N HCl MeOH, concentrated to solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (73 mg, 50%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.38). ^1H NMR (400 MHz, DMSO-d_6) δ8.21 (s, 1H), 8.18 (dd, J=8.0,2.0 Hz. 1H), 7.59 (d, J=8.0 Hz, 1H), 3.43 (br s, 2H), 3.28 (m, 2H), 3.07 (dd, J=13.0, 13.0 Hz, 2H), 2.24 (m, 1H), 2.08 (d, J=11.5 Hz, 1H). APCI MS m/e 205.1 [(M+1)$^+$] mp 265–270° C.

EXAMPLE 8

4-AMINO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

4-Nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3.5-triene (500 mg, 2.08 mmol) was stirred in 1,4-dioxane (40 mL) and treated with saturated aqueous Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (1.8 g, 8.31 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4×30 mL), dried through a cotton plug and concentrated to provide an oil (500 mg, 91%).

This oil (500 mg, 1.64 mmol) was dissolved in MeOH (30 mL), treated with 10% Pd/C (~50 mg) and hydrogenated under a H_2 atmosphere (45 psi) for 1 hour. The mixture was filtered through a Celite pad and concentrated to a clear oil (397 mg, 88%)

This oil (50 mg, 0.18 mmol) was stirred in 3N HCl EtOAc (3 mL) for 2 hours then concentrated to a white solid (25 mg, 56%). ^{1}H NMR (400 Mhz, DMSO-d_6) δ7.38–7.10 (3H), 3.60 (br s, 2H), 3.25 (m, 2H), 2.98 (m, 2H), 2.18 (m, 1H), 1.98 (d, J=11.5 Hz, 1H). APCI MS m/e 175.1 [(M+1)$^+$] mp 189–192° C.

EXAMPLE 9

N^1-[10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN4-YL]ACETAMIDE HYDROCHLORIDE

A) 1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone

Hydrogenation of 1-(4-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)2.2.2-trifluoro-ethanone (2.0 g, 6.66 mmol) under a H_2 atmosphere (40 psi) and 10% Pd/C (200 mg) in MeOH over 1.5 hours, filtration through Celite and concentration affords a yellow oil (1.7 g). (TLC 50% EtOAc/hexanes R_f0.27). ^{1}H NMR (400 MHz, $CDCl_3$) δ6.99 (m, 1H), 6.64 (br s, 1H), 6.57 (m, 1H), 4.25 (m, 1H), 3.82 (m, 1H), 3.50 (m, 1H), 3.17–3.07 (m, 3H), 2.35 (m, 1H), 1.90 (d, J=10.8 Hz, 1H). GCMS m/e 270 (M$^+$).

B) N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-acetamide

1-(4-Amino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (850 mg, 3.14 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with triethyl amine (0.53 mL, 3.76 mmol) and acetyl chloride (0.23 mL, 3.2 mmol) then stirred 18 hours. Standard $NaHCO_3$ workup yielded an oil which was chromatographed to provide a clear oil (850 mg, 87%). (50% EtOAc/hexanes R_f0.28).

C) N^1-[10-Azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien4-yl]acetamide hydrochloride

N-(10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien4-yl)-acetamide (100 mg, 0.32 mmol) was stirred with Na_2CO_3 (70 mg, 0.64 mmol) in MeOH (10 mL) and H_2O (2 mL) at 70° C. for 18 hours. The mixture was concentrated, water was added and the product was extracted with EtOAc. The organic layer was extracted with 1N aqueous HCl (3×20 mL) and the acidic layer washed with EtOAc (2×20 mL). The aqueous layer was basified to pH ~10 with Na_2CO_3 (s) and product was extracted with EtOAc (3×20 mL). The organic layer was dried (sodium sulfate (Na_2SO_4)) and concentrated to an oil. This material was dissolved in MeOH and treated with 3N HCl EtOAc (3 mL), concentrated and recrystallized from MeOH/Et_2O to provide a solid (40 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.98 (s, 1H), 9.02 (br m, NH), 7.65 (s, 1H), 7.55 (br s, NH), 7.36 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 3.33 (m, 4H), 2.96 (m, 2H), 2.13 (m, 1H), 2.00 (s, 3H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 217.2 [(M+1)$^+$]. mp 225–230° C.

EXAMPLE 10

6-METHYL-5-THIA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) N-(10-Trifluorothioacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)thioacetamide

N-(10-Trifluoroacetyl-10-aza-tricyclo[6 3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thioacetamide (850 mg, 2.72 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.1 g, 2.72 mmol) were combined in toluene (10 mL) and brought to reflux for 1.5 hours. After cooling the reaction was worked up with EtOAC/saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to produce product (410 mg, 44%). (50% EtOAc/hexanes R_f 0.38)

B) 6-Methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene hydrochloride

The above oil, 2,2,2-trifluoro-N-(10-trifluorothioacetyl-10-azatrcyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-thoacetamide, (360 mg, 1.05 mmol) was dissolved in MeOH (10 mL) and 1N NaOH (5 mL) and added to potassium ferricyanide ($K_3Fe(CN)_6$)(1.72 g, 5.23 mmol) in H_2O (10 mL). This mixture was warmed to 60° C. for 1.5 hours, cooled, concentrated and worked up with EtOAc/H_2O. This material was stirred in dioxane (20 mL) and treated with H_2O (50 mL)) and Na_2CO_3 to achieve pH 10. To this was added di-t-butyldicarbonate (436 mg, 2.0 mmol) and the mixture was stirred for 18 hours. The reaction was concentrated, treated with H_2O and extracted with CH_2Cl_2. The product was chromatographed (Silica 30% EtOAc/hexanes R_f0.41) to yield an oil (100 mg).

The above product was treated with 3N HCl/EtOAc (3 mL) and warmed to reflux for ~15 minutes then concentrated to a solid which was azeotroped with CH_2Cl_2 (2×). These solids were dissolved in a minimum amount of MeOH then saturated with Et_2O and stirred, The resulting white crystalline powder was collected by filtration (40 mg, 14%).

^{1}H NMR (400 MHz, DMSO-d_6) δ9.46 (s, NH), 7.65 (s, 1H), 7.82 (s, 1H), 7.65 (br m, NH), 3.36 (m, 2H), 3.24 (m, 2H), 3.02 (m, 2H), 2.76 (s, 3H), 2.23 (m, 1H), 2.06 (d, J=10.8 Hz, 1H). APCI MS m/e 231.1 [(M+1)$^+$] mp 183–184° C.

EXAMPLE 11

4,5-DINITRO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE

A) 1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-2,2,2-trifluoroethanone (Based on the method described in Coon, C. L.; Blucher. W. G.; Hill, M. E. *J. Org. Chem.* 1973, 25, 4243. For an additional related example of dinitration see: Tanida, H.; Ishitobi, H.; Irie, T.; Tsushima, T. *J. Am. Chem. Soc.* 1969, 91, 4512.)

To a solution of trifluoromethanesulfonic acid (79.8 ml, 902.1 mmol) in CH_2Cl_2 (550 ml) stirred at 0° C. was slowly added nitric acid (19.1 ml, 450.9 mmol) generating a white precipitate. After 10 minutes, 1-(10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (50 g, 196 mmol) in CH_2Cl_2 (300 ml) was added dropwise from an addition funnel over 30 minutes. The reaction was stirred at 0° C. for 2.5 hours and then stirred at room temperature for 24 hours. The reaction mixture was poured into a vigorously stirred mixture of H_2O (500 ml) and ice (400 g). The layers were separated and the aqueous layer back extracted with CH_2Cl_2 (3×300 ml). The organic layer was combined and

washed with H_2O (3×300 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (2×100 ml). The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution (200 mL) and H_2O (200 mL) then dried through a cotton plug and concentrated to solids. Trituration with EtOAc/hexanes produced off white solids which were filtered and dried (52 g, 151 mmol, 77%. The mother liquor was chromatographed to give an additional 4.0 g for a total of 56.0 g (82.8%). (TLC 50% EtOAc/hexanes R_f0.29) ^1H NMR (400 MHz, $CDCl_3$) δ7.77 (s, 1H), 7.75 (s, 1H), 4.39 (br d, J=13.0 Hz, 1H), 3.98 (br d, J=13.0 Hz, 1H), 3.65 (d, J=13.0 Hz, 1H), 3.49 (br s, 1H), 3.44 (br s, 1H), 3.24 (br d, J=12.6 Hz, 1H), 2.53 (m, 1), 2.14 (d, J=11.5 Hz, 1H). GCMS m/e 345 (M^+).

B) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-triflouroethanone (3.7 g, 10.7 mmol) and Na_2CO_3 (2.3 g, 21.4 mmol) were combined in MeOH (50 mL)) and H_2O (20 mL) then warmed to reflux for 18 hours. The reaction was cooled, concentrated, treated with H_2O and extracted with CH_2Cl_2 (3×50 mL) then dried through a cotton plug. After concentration. the residue was chromatographed to provide brown solids. (1.9 g. 71%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.36). ^1H NMR (400 MHz, $CDCl_3$) δ7.69 (s, 2H), 3.17 (br s, 2H), 3.11 (d, J=12.6 Hz, 2H), 2.53 (m, 1H), 2.07 (d, J=11.0 Hz, 1H). GCMS m/e 249 (M^+).

EXAMPLE 12

6-METHYL-7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene, (1.9 g, 7.6 mmol) was stirred in 1,4-dioxane (75 mL) and treated with saturated aqueous Na_2CO_3 solution (10 mL). To this was added di-t-butyldicarbonate (3.31 g, 15.2 mmol). After stirring 6 hours the reaction was treated with H_2O (50 mL) and extracted with EtOAc (4×25 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide product (1.9 g, 71%). (TLC 30% EtOAc/hexanes (NH_3) R_f0.58). ^1H NMR (400 MHz, $CDCl_3$) δ7.77 (br s, 1H), 7.72 (br s, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 3.39 (br s, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.18 (m, 1H), 2.46 (m, 1H), 2.02 (d, J=11.0 Hz, 1H).

B) 4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7) 3,5-triene-10-carboxylic acid tert-butyl ester (1.9 g, 5.44 mmol) was hydrogenated in MeOH under a H_2 atmosphere (45 psi) over 10% Pd/C (100 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (1.5 7 g, 100%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.14).

C) 6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see: Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post, R. J. *Tetrahedron Lett.* 1993, 34, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (700 mg, 2.42 mmol) was dissolved in EtOH (10 mL) and acetic acid (HOAc) (1 mL) and treated with 1-ethoxyethylenemalononitrile (329 mg, 2.42 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3×50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (247 mg, 36%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.28).

D) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Pilarski, B. *Liebigs Ann. Chem.* 1983, 1078.)

6-Methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (80 mg, 0.267 mmol) was stirred in 50% aqueous NaOH solution (3 mL) and DMSO (1 mL) then treated with 1-iodopropane (0.03 mL, 0.321 mmol). This mixture was warmed to 40° C. for 2 hours then cooled, treated with H_2O and extracted with EtOAc. The organic layer was washed with H_2O (3×) then dried (Na_2SO_4), filtered and concentrated to an oil (90 mg,.0.253 mmol). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.15).

E) 6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,10}$]pentadeca-2(10),3,5,8-tetrane-13-carboxylic acid tert-butyl ester (90 mg, 0.253 mmol) was dissolved in 3N HCl EtOAc (5 mL) and warmed to 100° C. for ½ hour. The mixture was cooled, concentrated, slurried in EtOAc, and filtered to provide a white solid (25 mg, 34%). ^1H NMR (400 MHz, DMSO-d_6) δ9.56 (s, NH), 7.91 (s, 1H), 7.83 (br m, NH), 7.74 (s, 1H), 4.38 (m, 2H), 3.48 (m, 2H), 3.32 (m, 2H), 3.10 (m, 2H), 2.87 (s, 3H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H) 1.85 (m, 2H). 0.97 (m, 3H). mp 147–150° C.

EXAMPLE 13

5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester (For conditions, see; Segelstein, B. E.; Chenard, B. L.; Macor, J. E.; Post. R. J. *Tetrahedron Lett.* 1993, 34, 1897.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (1.0 g, 3.45 mmol) was dissolved in EtOH (10 mL) and HOAc (1 mL) and treated with ethoxymethylenemalononitrile (421 mg, 3.45 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated treated with H_2O and saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3×50 mL), then dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide brown solids (580 mg, 56%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f0.28)

B) 5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

5,7,13-Triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^1H NMR (400 MHz, D_2O) δ8.95 (s, 1H), 7.67 (s, 2H), 3.45 (br s, 2H), 3.31 (d, J=12.5 Hz, 2H), 3.13 (d, J=12.5 Hz, 2H), 2.30 (m, 1H), 1.99 (d, J=11.5 Hz, 1H). APCI MS m/e 200.1 [(M+1)$^+$]. mp>250° C.

EXAMPLE 14

7-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, D_2O) δ8.97 (s, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 3.94 (s, 3H), 3.48 (m, 2H), 3.33 (d, J=12.2 Hz, 2H), 3.14 (d, J=12.2 Hz, 2H), 2.34 (m, 1H), 2.03 (d, J=11.5 Hz, 1H). APCI MS m/e 214.2 [(M+1)$^+$].

EXAMPLE 15

6-METHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

6-Methyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.40 (br m, NH), 7.77 (br m, NH), 7.70 (s, 1H), 3.44 (m, 2H), 3.30 (m, 2H), 3.05 (br d, J=11.0 Hz, 2H), 2.79 (s, 3H), 2.23 (m, 1H), 2.10 (d, J=10.8 Hz, 1H). GCMS m/e 213.5 (M$^+$).

EXAMPLE 16

6,7-DIMETHYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 6-methyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodomethane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.52 (s, NH), 7.84 (s, 1H), 7.82 (br m, NH), 7.72 (s, 1H), 3.90 (s, 3H), 3.45 (m, 2H), 3.28 (m, 2H), 3.04 (m, 2H), 2.82 (s, 3H), 2.23 (m, 1H), 2.12 (d, J=11.0 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. mp 225–230° C.

EXAMPLE 17

7-PROPYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 12D, 5,7,13-triazatetracyclo[9.3.10^{2,10}.0^{4,8}]pentadeca-2(10)3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by reaction with iodopropane followed by deprotection as described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.52 (s, 1H), 9.45 (br s, NH), 7.97 (s, 1H), 7.85 (s, 1H), 7.83 (br m, NH), 4.43 (m, 2H), 3.49 (m, 2H), 3.33 (m, 2H), 3.08 (m, 2H), 2.28 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.92 (m, 2H), 0.93 (m, 3H). APCI MS m/e 242.2[(M+1)$^+$]. mp 170–171° C. (subl.).

EXAMPLE 18

7-BUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5,8-triene-10-carboxylic acid tert-butyl ester (For conditions, see; Senskey, M. D.; Bradshaw, J. D.; Tessier, C. A.; Youngs, W. J. *Tetrahedron Lett.* 1995, 36, 6217.)

4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (500 mg, 1.43 mmol) and 1-butylamine (1.42 mL, 14.3 mmol) were combined in THF (5 mL) and stirred 4 hours. The mixture was diluted with EtOAc (50 mL)) and washed with H_2O (3×30 mL.) then dried (Na_2SO_4), filtered and concentrated to an oil. This oil was passed through a Silica gel filter column to remove baseline impurities eluting with 30% EtOAc/hexanes (510 mg, 1.41 mmol, 99%).

B) 4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

4-Butylamino-5-nitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (460 mg, 1.27 mmol) was treated with ammonium formate (850 mg, 12.7 mmol) and 10% Pd(OH)$_2$/C (50 mg) in MeOH (20 mL) and brought to reflux for 1 hour then filtered through a Celite pad and concentrated. The solids were treated with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 (3×30 mL) and dried by filtration through a cotton plug to give an oil (440 mg, 100%).

C) 7-Butyl-5,7,13-triazatetracyclo[9.3.1^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Butylamino-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (440 mg, 1.27 mmol) was dissolved in EtOH (20 mL) and HOAc (3 mL) and treated with ethoxymethylenemalononitrile (186 mg, 1.52 mmol). The resulting mixture was warmed to 60° C. and stirred 18 hours. The reaction was cooled, concentrated, treated with H_2O and saturated aqueous Na_2CO_3 solution then extracted with EtOAc (3×50 mL) and dried (Na_2SO_4). After filtration and concentration, the residue was chromatographed to provide a yellow oil. (400 mg, 89%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.70).

D) 7-Butyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene hydrochloride

7-Butyl-5,7,13-triazatetracyclo[9.3.1^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.93 (brs, NH), 9.68 (s, 1H), 7.99 (s, 1H), 7.92 (br m, NH), 7.87 (s, 1H), 4.50 (m, 2H), 3.49 (m, 2H), 3.30 (m, 2H), 3.08 (m, 2H), 2.26 (m, 1H), 2.15 (d, J=11.0 Hz, 1H), 1.88 (m, 2H), 1.32 (m, 2H), 0.82 (t, J=7.0 Hz, 3H). APCI MS m/e 256.2 [(M+1)$^+$]. mp 204–208° C.

EXAMPLE 19

7-Isobutyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene hydrochloride

4,5-Dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and isobutylamine were converted to the title compound utilizing the methods described in Example 18A–D. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.74 (s, 1H), 7.52 (s, 1H), 7.14 (s, 1H), 3.90 (dd, J=7.5,2.0 Hz, 2H), 3.04–2.97 (m, 4H), 2.70 (dd, J=12,8.2,3 Hz, 2H) 2.42 (m, 1H), 2.19 (m, 1H), 1.98 (d, J=10.5 Hz, 1H), 0.93 (m, 6H). APCI MS m/e 256.2 [(M+1)$^+$]. mp 147–150° C. (subl.).

EXAMPLE 20

6-METHYL-7-ISOBUTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

A) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.0^{2,10}.0^{4,8}]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester

4-Amino-5-isobutylamino-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (250 mg, 0.74 mmol) from Example 19B was dissolved in EtOH (10 mL) and HOAC (3 mL) and treated with 1-ethoxyethylenemalononitrile (118 mg, 0.87 mmol). The reaction proceeded as in Example 18C (18 h) and was worked up similarly to provide product (TLC 3% MeOH/CH_2Cl_2 (NH_3) R_f0.57).

B) 6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene hydrochloride

6-Methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene-13-carboxylic acid tert-butyl ester was converted to the title compound by the methods described in Example 12E. APCI MS m/e 270.3 [(M+1)$^+$]. mp 129–130° C. (subl.).

EXAMPLE 21

7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A. 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to 4-phenylamino-5-nitro-10-aza-tricyclo[6.3.1.$0^{2,7}$] dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl at 75° C. for 4 hours in the coupling step. This was then converted to the title compound utilizing the methods described in Example 18B,C,D. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.08 (1H), 7.78–7.57 (m, 7H), 3.47–3.00 (m, 6H), 2.23 (m, 1H), 2.09 (d, J=11.5 Hz, 1H). APCI MS m/e 276.2 [(M+1)$^+$]. mp 210–213° C.

EXAMPLE 22

6-METHYL-7-PHENYL-5,7,13-TRIAZATETRACYCLO[9.3.$10^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 21 and Example 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and aniline were converted to the, title compound, ^{1}H NMR (400 MHz, DMSO-d_6) δ7.79 (s, 1H), 7.73–7.56 (m, 5H), 7.32 (s, 1H), 3.46–2.99 (m, 6H), 2.66 (s. 3H), 2.23 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). APCI MS m/e 290.2 [(M+1)$^+$]. mp>250° C.

EXAMPLE 23

7-NEOPENTYL-5,7,13-TRIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example 18A–D, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound, t-Boc precursor GCMS m/e 369 (M$^+$). (HCl salt) mp>250° C.

EXAMPLE 24

6-METHYL-7-NEOPENTYL-5,7,13-TRIAZATETRACYCLCO[9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10)3,5,8-TETRAENE HYDROCHLORIDE

Utilizing the methods described in Example, 21 and 20, 4,5-dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester and neopentylamine were converted to the title compound. ^{1}H NMR (400 MHz DMSO-d_6) δ7.31 (s, 1H), 7.27 (s, 1H), 7.02 (br s, NH), 4.41 (t, J=13.0 Hz, 2H), 3.90 (s, 3H), 3.47–3.26 (m, 6H), 2.20 (m, 1H), 2.00 (d, J=11.5 Hz, 1H), 0.90 (s, 9H), t-Boc precursor APCI MS m/e 384.2 [(M +1)$^+$]. mp>250° C.

EXAMPLE 25

6,7-DIMETHYL-5,8,14-TRIAZATETRACYCLO[10.3.$10^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE (Based on the following procedure: Jones. R. G.; McLaughlin, K. C. *Org. Syn.* 1963, 4, 824, b) Ehrlich. J., Bobert. M. T. *J. Org. Chem.* 1947, 522.)

4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (100 mg, 0.35 mmol) was warmed to 80° C. in H_2O (5 mL). To this butane 2,3-dione (0.034 mL, 0.38 mmol) was added under N_2 for 2 hours. The reaction was cooled to room temperature and extracted with EtOAc (3×40 ml). The combined organic layer was washed with H_2O (2×30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an oil (120 mg, 100%). The oil was dissolved in 2N HCl MeOH (5 mL) and warmed to reflux for 30 minutes, then concentrated. Recrystallization from MeOH/Et_2O provided a white powder (50 mg, 43%). (TLC EtOAc R_f0.14). ^{1}H NMR (400 MHz, DMSO-d_6) δ7.85 (s, 2H), 3.50 (br s, 2H), 3.32 (d, J=12.5 Hz, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.64 (s, 6H), 2.24 (m, 1H), 2.13 (d, J=11.0 Hz, 1H). t-Boc precursor APCI MS m/e 340.3 [(M+1)$^+$].

EXAMPLE 26

5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE HYDROCHLORIDE

A) 1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-triflouro-ethanone (3.0 g, 8.70 mmol) was hydrogenated in MeOH (30 ml) under H_2 (45 psi) over $Pd(OH)_2$ (300 mg of 20 wt %/C, 10% wt). After 2.5 hours the reaction was filtered through a Celite pad and rinsed with MeOH (30 ml). The solution was concentrated to a light brown oil which crystallized (2.42 g, 96%). (TLC 10% MeOH/CH_2Cl_2 R_f0.56). APCI MS m/e 286.2[(M+1)$^+$]. mp 129–131° C.

B) 1-(5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,9-pentaene)-2,2,2-trifluoro-ethanone

1-(4,5-Diamino-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoroethanone (500 mg, 1.75 mmol) was stirred in THF (2 ml). This mixture was treated with H_2O (2 mL) and glyoxal sodium bisulfite addition compound hydrate (931 mg, 3.50 mmol) then stirred at 55° C. for 2.5 hours. The reaction was cooled to room temperature and extracted with EtOAc (3×40 ml). The combined organic layer was washed with H_2O (2×30 ml), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel to provide an off white powder (329 mg, 60%). (TLC 25% EtOAc/hexanes R_f0.40). mp 164–166° C.

C) 5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene hydrochloride

1-(5,8,14-Triazatetracyclo(10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene)-2,2,2-trifluoro-ethanone (320 mg, 1.04 mmol) was slurred in MeOH (2.0 ml) and treated with Na_2CO_3 (221 mg, 2.08 mmol) in H_2O (2.0 ml). The mixture was warmed to 70° C. for 2 hours. then concentrated, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried through a cotton plug and concentrated to give a light yellow oil (183 mg, 83%) which solidified upon standing (mp 138–140° C.). This material

was dissolved in MeOH (10 mL), treated with 3M HCl/EtOAc (3 ml), concentrated and azeotroped with MeOH (2×20 mL) to give solids which were recrystallized from MeOH/Et_2O to afford product as a white solid (208 mg, 97%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.26). ^1H NMR (400 MHz, CD_3OD) δ8.94 (s, 2H), 8.12 (s, 2H), 3.70 (m, 2H), 3.54 (d, J=12.5 Hz, 2H), 3.35 (d, J=12.5 Hz, 2H), 2.49 (m, 1H), 2.08 (d, J=11.0 Hz, 1H). GCMS m/e 211 (M^+). mp 225–230° C.

EXAMPLE 27

14-METHYL-5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]HEXADECA-2(11),3.5.7.9-PENTAENE HYDROCHLORIDE

5,8,14-Triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene (207 mg, 0.98 mmol) was treated with 37% aqueous formaline solution (1 mL) and formic acid (1 mL) then warmed to 80° C. for 1 hour. The reaction was poured into water, made basic (NaOH, pH~11) and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and chromatographed on Silica gel to provide a yellow solid. This was stirred in MeOH (2 mL) and treated with 3N HCl EtOAc (2 mL). After concentration the solids were recrystallized from MeOH/Et_2O to afford product as a white solid (70 mg, 27%). (2% MeOH/CH_2Cl_2 (NH_3) R_f 0.47). ^1H NMR (400 MHz, $CDCl_3$) δ8.71 (s, 2H), 7.80 (s, 2H), 3.37 (br s, 2H), 3.03 (m, 2H), 2.47 (m, 2H), 2.32 (m, 1H), 2.18 (br s, 3H), 1.84 (d, J=11.0 Hz, 1H). APCI MS m/e 226.2 [(M+1)$^+$]. mp >250° C.

EXAMPLE 28

5-OXA-7,13-DIAZATETRACYCLO[9.3.1.$0^{2,10}$.$0^{4,8}$] PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

1-(4,5-Dinitro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (900 mg, 2.61 mmol) and potassium acetate (KOAc) (2.6 g, 26.1 mmol) were dissolved in DMSO (10 mL) and warmed with stirring to 100° C. for 16 hours. The mixture was cooled and diluted with H_2O (50 mL) then extracted with 80% EtOAc/hexanes (6×25 mL). The organic layer was washed with H_2O (3×20 mL), dried (Na_2SO_4), filtered and concentrated and purified by chromatography to give an oil (575 mg, 70%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.56)

B) 2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-nitro-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (575 mg, 1.82 mmol) was hydrogenated in MeOH under a H_2 atmosphere at (45 psi) over 10% Pd/C (80 mg) for 1.5 hours then filtered through a Celite pad and concentrated to white solids (450 mg, 86%). (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.6). ^1H NMR (400 MHz, CD_3OD) δ6.67–6.59 (m, 2H), 4.12 (m, 1H), 3.73 (m, 1H), 3.73 (m, 1H), 3.51 (m, 1H), 3.07 (m, 2H), 2.24 (m, 1H), 1.94 (d, J=10.5 Hz, 1H). GCMS m/e 286 (M^+).

C) 2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(1.0),3,6,8-tetraene)-ethanone (Goldstein, S. W.; Dambek, P. J. *J. Het. Chem.* 1990, 27, 335.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), trimethyl orthoformate (0.19 mL, 1.73 mmol) pyridinium-p-toluenesulfonic acid (PPTS, 18 mg, 0.07 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. The mixture was cooled, treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered, concentrated and purified by chromatography to give an oil (110 mg, 71%). (TLC 20% EtOAc/hexanes R_f 0.40)

D) 5-Oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3.6.8-tetraene)-ethanone (110 mg, 0.37 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (78 mg, 0.74 mmol) in H_2O (2 mL). The stirred mixture was warmed to 80° C. for 2 hours. concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The product was extracted into aqueous 1N HCl solution (2×40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. The product was extracted with EtOAc (3×40 mL), dried (Na_2SO_4), concentrated and chromatographed on Silica gel to produce an oil. (TLC 5% MeOH/CH_2Cl_2 (NH_3) R_f 0.19).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (55 mg, 63%). ^1H NMR (400 MHz, CD_3OD) δ8.47 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 3.41 (m, 2H), 3.30 (m, 2H), 3.10 (d, J=12.5 Hz, 2H), 2.47 (m, 1H), 2.15 (d, J=11.0 Hz, 1H). APCI MS m/e 201.03 [(M+1)$^+$]

EXAMPLE 29

6-METHYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

A) 2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo[9.3.1 $0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone (150 mg, 0.524 mmol), triethyl orthoacetate (0.34 mL, 1.83 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol) and xylenes (10 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. Workup, isolation and purification as in Example 28C provided the title compound (90 mg, 55%).

B) 6-Methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$] pentadeca-2(10),3,6,8-tetraene hydrochloride

2,2,2-Trifluoro-1-(6-methyl 5-oxa-7,13-diazatetracyclo [9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene)-ethanone (90 mg, 0.30 mmol) was stirred in MeOH (5 mL) and treated with Na_2CO_3 (61 mg, 0.58 mmol) in H_2O (3 mL). The stirred mixture was warmed to 80° C. for 2 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The solution was dried (Na_2SO_4), concentrated, and chromatographed on Silica gel to produce an oil. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.18). ^1H NMR (free base) (400 MHz, $CDCl_3$) δ7.40 (s, 1H), 7.26 (s, 1H), 3.05–2.98 (m, 4H), 2.72 (d, J=12.8 Hz, 2H), 2.59 (s, 3H), 2.46 (m, 1H), 1.98 (d, J=10.5 Hz, 1H).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) then concentrated, stirred in a minimum of CH_2Cl_2 and saturated with hexanes. After 18 hours, the product was collected by filtration (10 mg, 13%). APCI MS m/e 215.2 [(M+1)$^+$]. mp >250° C.

EXAMPLE 30

2-FLUORO-N-(5-HYDROXY-10-AZA-TRICYCLO [6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIEN-4-YL)-BENZAMIDE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-ethanone(150 mg, 0.524 mmol), 2-fluorobenzoyl chloride (0.07 mL, 0.576 mmol), pyridinium-p-toluenesulfonic acid (PPTS, 20 mg, 0.08 mmol), pyridine (0.046 mL, 0.576 mmol) and xylenes (5 mL) were combined under nitrogen and stirred at 135° C. for 18 hours. After 24 hours, additional PPTS (50 mg) was added and the material stirred at 135° C. for an additional 24 hours. Workup as above provided crude product (145 mg, 0.375 mmol) which was combined with Na_2CO_3(s) (80 mg, 0.75 mmol) in MeOH (5 mL) and H_2O (2 mL) and heated to reflux. After 3 hours, the reaction was cooled and diluted with water then extracted with CH_2Cl_2 (4×40 mL), dried through a cotton plug then chromatographed to remove baseline impurity (5% MeOH/CH_2Cl_2 (NH_3)). The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of MeOH and the solution was saturated with Et_2O and stirred. After stirring 4 hours the product was collected by filtration (85 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ7.99 (m, 2H), 7.59 (m, 1H), 7.36–7.23 (m, 2H), 6.82 (s, 1H), 2.99 (m, 4H), 2.78 (m, 2H), 2.35 (m, 1H), 1.96 (d, J=10.5 Hz, 1H). APCI MS m/e 313.1 [(M+1)$^+$]. mp 125–130° C. (subl.).

EXAMPLE 31

4-CHLORO-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Copper(I)chloride (CuCl) was prepared as follows: $CuSO_4$ (4.3 g) and NaCl (1.2 g) were dissolved in hot H_2O (14 mL). sodium bisulfite ($NaHSO_3$) (1 g) and sodium hydroxide (NaOH) (690 mg) were dissolved in H_2O (7 mL) and added to the hot acidic solution over 5 minutes. The precipitated white solids were filtered and washed with water.

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (460 mg, 1.7 mmol) was dissolved in H_2O (3 mL) and concentrated HCl solution(1 mL) then cooled to 0° C. and treated with a solution of sodium nitrite ($NaNO_2$) (275 mg) in H_2O (1 mL) dropwise. To the resulting solution was added a CuCl (202 mg, prepared as described above, 2.04 mmol) in concentrated HCl solution (2 mL) over 10 minutes (gas evolution observed). The resulting solution was warmed to 60° C. for 15 minutes, then was cooled to room temperature and extracted with EtOAc (4×30 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to an oil which was filtered through a Silica pad to remove baseline material eluting with 50% EtOAc/hexanes to give an oil (470 mg, 95%).

B) 4-Chloro-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene hydrochloride

1-(4-Chloro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (470 mg, 1.62 mmol) and Na_2CO_3 (344 mg, 3.24 mmol) in MeOH (30 mL) and H_2O (10 mL) were heated to reflux. After 2 hours, the reaction was cooled and diluted with water then extracted with EtOAc (4×40 mL), dried (Na_2SO_4), filtered and concentrated to a yellow oil. The crude material was treated with excess 3N HCl EtOAc and concentrated, then dissolved in a minimum of CH_2Cl_2 and the solution was saturated with hexanes and stirred, After stirring 4 hours the product was collected by filtration (155 mg, 42%). ^{1}H NMR (free base) (400 MHz, $CDCl_3$) δ7.15 (m, 2H), 7.09 (d, J=8.0 Hz, 1H), 3.00–2.94 (m, 4H), 2.68, (m, 2H), 2.38 (m, 1H), 1.92 (d, J=10.5 Hz, 1H). ^{1}H NMR (HCl salt) (400 MHz, DMSO-d_6) δ7.30–7.20 (m, 3H), 3.30–3.15 (m, 6H), 2.37 (m, 1H), 1.89 (d, J=11.0 Hz, 1H). APCI MS m/e 194.1 [(M+1)$^+$].

EXAMPLE 32

10-AZATRICYCLO[6.3.1.0~2.7~]DODECA-2(7),3,5-TRIEN-4-YL CYANIDE HYDROCHLORIDE

A) 1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(4-Amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (500 mg, 1.85 mmol) was dissolved in H_2O (5 mL) and concentrated H_2SO_4 solution (0.5 mL) then cooled to 0° C. and treated with a solution of sodium nitrite ($NaNO_2$) (140 mg, 2.04 mmol) in H_2O (3 mL) dropwise. Potassium iodide (460 mg, 2.78 mmol) in 1N H_2SO_4 solution (0.5 mL) was added over 10 minutes (reaction becomes dark red). The resulting solution was warmed to room temperature and stirred 18 hours. The reaction was quenched with $NaHSO_3$ and water (pH 2.5) then extracted with EtOAc (4×30 mL). After drying (Na_2SO_4), the solution was filtered and concentrated to a yellow oil which was chromatographed on Silica gel to provide a yellow oil. (260 mg, 37%). (TLC 30% EtOAc/hexanes R_f 0.70). (A 5.4 g scale performed as above yielded 5 g, 67%).

B) 4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (5 g, 13.1 mmol) and 37% saturated aqueous NH_4OH solution (50 mL)) were stirred in MeOH (250 ml) for 2 hours then concentrated and azeotroped with MeOH (2×50 mL). The resulting product was stirred in 1,4-dioxane (75 mL) and treated with saturated Na_2CO_3 solution (15 mL). To this was added di-t-butyldicarbonate (5.71 g, 26.2 mmol). After stirring 18 hours the reaction was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (4×30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed on Silica gel (TLC 20% EtOAc/hexanes) to provide product as an oil (4.9 g, 98%).

C) 4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (Utilizing the methods described in: House, H. O.; Fischer, W. F. *J. Org. Chem.* 1969, 3626.)

CuCN (108 mg, 1.21 mmol) and NaCN (59 mg, 1.21 mmol) were combined in dry DMF (6 mL) and warmed to 150° C. under N_2. Solution occurs in 20 minutes. To this was added 4-iodo-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (232 mg, 0.6 mmol) in DMF (3.5 mL) and the mixture was stirred for 18 hours at 150° C., The reaction was cooled and diluted with 50% saturated aqueous NaCl solution and extracted with 50% EtOAc/hexanes (3×30 mL). After drying (Na_2SO_4), filtration and concentration the product was isolated by chromatography (86 mg.. 50%). (TLC 20% EtOAc/hexanes R_f 0.28).

D) 10-Azatricyclo[6.3.1.0~2,7~]dodeca-2(7),3,5-trien-4-yl cyanide hydrochloride

4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester was treated with 3N HCl EtOAc (6 mL) and warmed to reflux for 2 hours, then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (49 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ9.66 (br s, NH), 7.86 (br s, NH), 7.74–7.70 (m, 2H), 7.49 (d, J=7.5 Hz, 1H), 3.33–2.97 (m,

6H), 2.17 (m, 1H), 2.01 (d, J=11.0 Hz, 1H). GCMS m/e 184 (M^+). mp 268–273° C.

EXAMPLE 33

3-(10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL)-5-METHYL-1,2,4-OXADIAZOLE HYDROCHLORIDE

4-Cyano-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (300 mg, 1 1 mmol) was stirred in EtOH (10 mL). To this hydroxyl amine hydrochloride (382 mg, 5.5 mmol) and NaOH (242 mg, 6.05 mmol) were added and the mixture was warmed to reflux. After 45 minutes, the reaction was cooled, diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford a yellow solid (110 mg, 0.35 mmol). This solid was dissolved in pyridine (1 mL) and treated with acetyl chloride (0.03 mL, 0.415 mmol) and warmed to 100° C. for 18 hours. The reaction was cooled, treated with H_2O and extracted with EtOAc. The organic extracts were washed with water and saturated aqueous NaCl solution, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel afforded product (50 mg, 0.15 mmol). (25% EtOAc/hexanes R_f 0.18). This product was treated with 2N HCl MeOH (10 mL), heated to 70° C. for 1 hour, cooled, concentrated and recrystallized from MeOH/Et_2O to provide product (15 mg). APCI MS m/e 242.2 [$(M+1)^+$].

EXAMPLE 34

1-(10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-YL)-1-ETHANONE HYDROCHLORIDE

A) 1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

1-(10-Aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2trifluoro-ethanone (253 mg, 1.0 mmol) and AcCl (0.68 mL, 10 mmol) were dissolved in DCE (3 mL) and treated with aluminum chloride ($AlCl_3$) (667 mg, 5.0 mmol). The resulting yellow mixture was stirred for 30 minutes then poured over ice and saturated aqueous $NaHCO_3$ solution. After stirring 20 minutes the mixture was extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried through a cotton plug then concentrated to a orange-yellow oil (255 mg, 86%).

B) 4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.3 g, 4.37 mmol) and 37% aqueous NH_4OH solution (10 mL) were stirred in MeOH (30 ml) for 3 hours, then concentrated and azeotroped with MeOH (2×50 mL). (This product could be converted to an HCl salt directly: see the next example.) The resulting product was stirred in 1,4-dioxane (20 mL) and treated with saturated aqueous Na_2CO_3 solution (5 mL). To this was added di-t-butyldicarbonate (1.91 g, 8.74 mmol). After stirring 2 hours, the reaction was treated with H_2O (50 mL), extracted with CH_2Cl_2 (4×30 mL), dried (Na_2SO_4), filtered, concentrated and chromatographed to provide an oil (1.3 g, 100%). (TLC 40% EtOAc/hexanes R_f 0.56).

C) 1-(10-Azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-yl)-1-ethanone hydrochloride

4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester (190 mg, 0.63 mmol) was treated with excess 3N HCl EtOAc and warmed to 70° C. for 1 hour then concentrated and dissolved in a minimum of MeOH. The resulting solution was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (81 mg, 54%). ^1H NMR (400 MHz, DMSO-d_6) δ9.75 (br s, NH), 7.89 (s, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.74 (br s, NH), 7.44 (d, J=8.0 Hz, 1H), 3.33 (br s, 2H), 3.22 (br s, 2H), 3.00 (br m, 2H), 2.5 (s, 3H), 2.17 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). GCMS m/e 201 (M^+). mp 198–202

EXAMPLE 35

10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIEN-4-OL HYDROCHLORIDE

A) Acetic acid 10-trifluoroacetyl-10-aza-tricyclo [6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester

1-(4-Acetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (2.5 g, 8.41 mmol) and 3-chloroperoxybenzoic acid (m-CPBA) (7.5 g, 42 mmol) were stirred in CH_2Cl_2 (20 mL) and warmed to 40° C. for 18 hours. The mixture was cooled to room temperature, then treated with dimethylsulfide (Me_2S) (3 mL, 40.8 mmol) and stirred 24 hours. The resulting mixture was poured into ice and saturated aqueous Na_2CO_3 solution (100 mL) then extracted with Et_2O (4×40 mL). The organic layer was washed saturated aqueous Na_2CO_3 solution (3×40 mL) then dried (Na_2SO_4), filtered and concentrated to afford an oil (1.83 g, 69%). (TLC EtOAc R_f 0.80).

B) 2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo [6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester (900 mg, 2.87 mmol) was stirred in MeOH (20 mL) and saturated aqueous $NaHCO_3$ solution (15 mL) for 48 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3×20 mL) then dried through a cotton plug. Chromatography on Silica gel provided pure product (420 mg, 54%). (TLC 5% MeOH/CH_2Cl_2 R_f 0.44). ^1H NMR (400 MHz, $CDCl_3$) δ7.05 (m, 1H), 6.70 (m, 1H), 6.62 (m, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.48 (m, 1H), 3.21 (br s, 1H), 3.16 (br s, 1H), 3.09 (m, 1H), 2.38 (m, 1H), 1.97 (d, J=11.0 Hz, 1H).

C) 10-Azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-4-ol hydrochloride

2,2,2-Trifluoro-1-(4-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-ethanone (50 mg, 0.184 mmol) was dissolved in MeOH/H_2O (3/1, 5 mL), treated with Na_2CO_3(s) (40 mg, 0.369 mmol) and warmed to 65° C. for 2 hours. The mixture was concentrated, diluted with H_2O and extracted with CH_2Cl_2 (3×20 mL) then dried through a cotton plug. Filtration through a Silica gel plug provided an oil (10% MeOH/CH_2Cl_2) which was treated with 3N HCl EtOAc (3 mL) then concentrated, dissolved in a minimum of MeOH which was saturated with Et_2O and stirred. After 18 hours the white crystalline product was collected by filtration (10 mg, 26%). ^1H NMR (400 MHz, $CDOD_3$) δ7.16 (d, J=8.0 Hz, 1H), 6.80 (d, J=2.0 Hz, 1H), 6.72 (dd, J=8.0,2.0 Hz, 1H), 3.32–3.28 (4H), 3.09 (dd, J=14.5, 12.0 Hz, 2H), 2.32 (m, 1H) 2.03 (d, J=11.0 Hz, 1H) APCI MS m/e 176.2 [$(M+1)^+$]. mp 308 (dec.) °C.

EXAMPLE 36

7-METHYL-5-OXA-6,13-DIAZATETRACYCLO [9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2,4(8),6,9-TETRAENE HYDROCHLORIDE

A) 1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone

Acetic acid 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}] dodeca-2(7),3,5-trien-4-yl ester (800 mg, 2.55 mmol) was combined with $AlCl_3$ (1.0 g, 7.65 mmol) and warmed to

170° C. for 2 hours. The mixture was cooled and treated with 1N aqueous HCl solution (20 mL), extracted with EtOAc and dried (Na_2SO_4). Chromatography affords an oil (190 mg, 24%). (TLC EtOAc R_f 0.75). ^1H NMR (400 MHz, $CDCl_3$) δ12.58 (s, 0.5H), 12.52 (s, 0.5H), 7.53 (s, 1H), 6.86 (s, 1H), 4.33 (m, 1H), 3.91 (m, 1H), 3.56 (m, 1H), 3.28 (br s, 1H), 3.24 (br s, 1H), 3.14 (m, 1H), 2.35 (m, 1H), 1.97 (br d, J=11.2 Hz, 1H).

B) 2,2,2-Trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone

1-(4-Acetyl-5-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (190 mg, 0.605 mmol), hydroxylamine HCl (99 mg, 1.21 mmol) and NaOAc (118 mg, 1.21 mmol) were combined in MeOH (4 mL) and H_2O (1 mL) and warmed to 65° C. for 18 hours. The mixture was cooled, diluted with H_2O and extracted with EtOAc which was dried (Na_2SO_4), filtered and concentrated to provide a yellow oil (177 mg, 93%).

C) 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0_{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone

The above oil, 2,2,2-trifluoro-1-[4-hydroxy-5-(1-hydroxyimino-ethyl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl]-ethanone (177 mg, 0.54 mmol) was stirred in DCE (3 mL), treated with triethylamine (0.4 mL, 2.8 mmol) and acetic anhydride (Ac_2O) (0.3 mL, 2.8 mmol) then stirred 18 hours. The reaction was treated with H_2O and extracted with EtOAc. The extracts were dried (Na_2SO_4), filtered and concentrated to a yellow oil which was dissolved in anhydrous DMF (3 mL) and treated with 60% NaH in oil (32 mg, 1.08 mmol). After stirring 18 hours, additional 60% NaH in oil was introduced (33 mg) and the mixture was stirred 2 hours. The reaction was quenched with H_2O (5 mL) and extracted with 80% EtOAc/hexanes (3×30 mL). The organic layer was washed with H_2O (3×20 mL), dried (Na_2SO_4), filtered and concentrated and chromatographed to provide an oil (40% EtOAc/hexanes R_f 0.56).

D) 7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene hydrochloride

Utilizing the methods described in Example 9C, 2,2,2-Trifluoro-7-Methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene-ethanone was converted to the title compound. This was treated with 3N HCl EtOAc (3 mL), concentrated and dissolved in a minimum of CH_2Cl_2 which was saturated with hexanes and stirred. After 18 hours the white crystalline product was collected by filtration (18 mg, 13% overall). ^1H NMR (400 MHz, DMSO-d_6) δ7.72 (s, 1H), 7.63 (s, 1H), 3.42–2.98 (m, 6H), 2.50 (s, 3H), 2.23 (m, 1H), 2.08 (d, J=10.5 Hz, 1H). APCI MS m/e 215.2 [(M+1)$^+$].

EXAMPLE 37

4-(2-Methyl-2H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride and 4-(1-Methyl-1H-pyrazol-3-yl)-10-aza-tricyclo[6.3.1.$0^{2,7}$dodeca-2(7),3,5-triene hydrochloride

1-(4-Acetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (1.0 g, 3.3 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (4.0 g, 33.6 mmol) were warmed to 140° C. for 18 hours. After cooling, a crystalline precipitate was filtered and rinsed with EtOAc (690 mg, 58%).

The above solid, 3-dimethylamino-1-(10-trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-propenone, (200 mg, 0.56 mmol) was dissolved in EtOH (3 mL) and treated with 5N HCl EtOH (0.1 mL) followed by methyl hydrazine (0.6 mmol). The resulting mixture was warmed to 70° C. for 4 hours. The mixture was cooled, diluted with water and extracted with EtOAc, dried (Na_2SO_4) and concentrated. Chromatography on Silica gel provided a 3/1 mixture of regioisomeric products (130 mg, 68%). (TLC 50% EtOAc/hexanes R_f 0.40).

The above oil (130 mg, 0.388 mmol) and Na_2CO_3(s) (82 mg, 0.775 mmol) were stirred in MeOH (10 mL) and H_2O (5 mL) for 18 hours. After cooling the reaction was diluted with water, extracted with CH_2Cl_2 dried through a cotton plug and concentrated. The product was purified by chromatography on Silica gel and concentrated to an oil. The salt was generated with 2N HCl MeOH, concentrated and recrystallized from MeOH/EtOAc to provide a 3/1 mixture of regioisomeric pyrrazoles (85 mg, 58%). (5% MeOH/CH_2Cl_2 (NH_3) R_f 0.25). TFA-precursor APCI MS m/e 336.2 [(M+1)$^+$].

EXAMPLE 38

4,5-DICHLORO-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (Based on Campaigne, E.; Thompson, W. *J. Org. Chem.* 1950, 72, 629.)

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (539 mg, 2.1 mmol) was stirred in CH_2Cl_2 (5 mL) and treated with ICl_3 (s) (982 mg, 4.21 mmol). The resulting orange solution was stirred 0.5 hours, poured into saturated aqueous $NaHSO_3$ solution (25 mL), extracted with CH_2Cl_2 (3×25 mL), dried through a cotton plug and concentrated to an oil (570 mg, 84%) (TLC 50% EtOAc/hexanes R_f 0.62).

B) 4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

1-(4,5-Dichloro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (570 mg, 1.75 mmol) was stirred in MeOH (25 mL) and treated with Na_2CO_3(s) (5 g, 47 mmol) in H_2O (5 mL). The stirred mixture was warmed to 70° C. for 4 hours, concentrated to solids, diluted with H_2O and extracted with EtOAc (3×40 mL). The product was extracted into 1N aqueous HCl solution (2×40 mL) which was washed with EtOAc then neutralized with saturated aqueous Na_2CO_3 solution to pH~10. Product was extracted with CH_2Cl_2 (3×40 mL), filtered through a cotton plug and concentrated to an oil (400 mg, 100%).

The oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL) and concentrated, then dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration (210 mg, 45%). (TLC 50% EtOAc/hexanes (NH_3) R_f 0.08). ^1H NMR (400 MHz, DMSO-d_6) δ7.58 (s, 2H), 3.33–2.97 (m, 6H), 2.18 (m, 1H), 1.99 (d, J=10.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ141.02, 130.60, 126.58, 45.54, 40.55, 38.30. GCMS m/e 227, 229 (M$^+$). mp 283–291° C.

EXAMPLE 39

N^4,N^4-DIMETHYL-10-AZATRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE-4-SULFONAMIDE HYDROCHLORIDE

A) 10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-sulfonyl chloride

1-(10-Aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-2,2,2-trifluoro-ethanone (530 mg, 2.1 mmol) was added

to chlorosulfonic acid (2 mL, 30 mmol) and stirred for 5 minutes. The mixture was quenched with ice, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to provide an oil (640 mg, 87%). (TLC 30% EtOAc/hexanes R_f 0.15).

B) N^4,N^4-Dimethyl-10-azatricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-sulfonamide hydrochloride

10-Trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) was stirred in THF (10 mL) and treated with 40% Me_2NH/H_2O (1.5 mL). After 10 minutes the mixture was concentrated and chromatographed on Silica gel (TLC 30% EtOAc/hexanes R_f 0.31) to provide an oil (256 mg, 78%). This material was dissolved in MeOH (6 mL) and NH_4OH (2 mL) and stirred 18 hours. The mixture was concentrated and azeotroped from MeOH (3×). The resulting oil was dissolved in MeOH and treated with 3N HCl EtOAc (4 mL), concentrated, dissolved in a minimum of MeOH and which was saturated with Et_2O and stirred 18 hours. The product was collected by filtration as a white powder (163 mg, 59%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.54). ^{1}H NMR (data, free base) (400 MHz, $CDCl_3$) δ7.64 (m, 2H), 7.41 (d, J=8.0 Hz, 1H), 3.30 (m, 2H), 3.20 (d, J=12.5 Hz, 2H), 3.07 (dd, J=12.5, 2.2 Hz, 2H), 2.69 (s, 6H), 2.45, (m, 1H), 2.00 (d, J=11.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ128.43, 124.16, 122.75, 46.67, 46.55, 42.11, 39,44, 37,81. GCMS m/e 266 (M^+). (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ7.68–7.52 (3H), 3.38 (m, 2H), 3.24 (m, 2H), 3.04 (m, 2H), 2.58 (s, 6H), 2.22 (m, 1H), 2.04 (d, J=11.0 Hz, 1H). GCMS m/e 266 (M^+). Anal. Calcd. for $C_{13}H_{18}N_2O_2HCl$: C, 51.56; H, 6.32; N, 9.25. Found C, 51.36; H, 6.09; N, 9.09.

EXAMPLE 40

4-(1-PYRROLIDINYLSULFONYL)-10-AZATRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The pyrrolidine analogue was prepared from 10-trifluoroacetyl-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-4-sulfonyl chloride (320 mg, 0.9 mmol) as by substituting pyrroline in the coupling step described in Example 39B. The TFA product was isolated as an oil (314 mg, 89%). Deprotection and conversion to the salt as in Example 39B affords a white powder (189 mg, 63%). (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.60). (TLC 50% EtOAc/hexanes R_f 0.65). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.66 (d, J=8.0 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J=8.0 Hz, 1H), 3.30–3.15 (m, 8H), 3.00 (m, 2H), 2.39 (m, 1H), 1.98 (d, J=11.5 Hz, 1H), 1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ146.91, 144 08, 136.65, 127.90, 124.18, 122.36, 50.43, 47.87, 46.80, 46.63, 42.11, 39.63, 25.10. APCI MS m/e 293 [(M+1)$^+$]. (data HCl salt) ^{1}H NMR (400 MHz, DMSO-d_6) δ9.78 (br s, NH), 8.1 (br s, NH), 7.73 (d, J =1.5 Hz, 1H), 7.66 (dd, J=8.0, 1.5 Hz, 1H), 7.53 (d, J=8.0 Hz, 1H), 3.39–3.01 (10H), 2.21 (m, 1H), 2.04 (d, J=11.0 Hz, 1H), 1.66 (m, 4H). GCMS m/e 292 (M^+). Anal. Calcd. For $C_{13}H_{18}N_2O_2HCl.1/2MeOH$: C, 54.07; H, 6.47; N, 8.51. Found C, 53.98; H, 6.72; N, 8.12.

EXAMPLE 41

5,13-DIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2,4(8),9-TRIEN-6-ONE HYDROCHLORIDE (The title compound was prepared following the procedures described in Quallich, G. J.; Morrissey, P. M. *Synthesis* 1993, 51–53, treating 4,5-dinitro-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-triene-10-carboxylic acid tert-butyl ester as an equivalent to an ortho fluoro phenyl moiety.) ^{1}H NMR (400 MHz, DMSO-d_6) δ10.42 (s, NH), 9.88 (br s, NH), 7.52 (br s, 1H), 7.15 (s, 1H), 6.79 (s, 1H), 3.41 (d, J=5.0 Hz, 2H), 3.35–3.13 (m, 4H), 2.93 (m, 2H), 2.12 (m, 1H), 1.95 (d, J=11.5 Hz, 1H). APCI MS m/e 215.2 [(M+1)$^+$].

EXAMPLE 42

6-OXO-5-OXA-7,13-DIAZATETRACYCLO[9.3.1.0^{2,10}.0^{4,8}]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE (For references, see: Nachman, R. J. *J. Het. Chem.* 1982, 1545.)

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo[6.3.1.0^{2,7}]dodeca-2(7),3,5-trien-10-yl)-ethanone (317 mg, 1.11 mmol) was stirred in THF (10 mL), treated with carbonyldiimidazole (269 mg, 1.66 mmol) and warmed to 60° C. for 18 hours. The mixture was concentrated, diluted with CH_2Cl_2 (50 mL) and washed with 1N aqueous HCl solution (3×10 mL). The organic layer was dried through a cotton plug, concentrated and chromatographed on Silica gel (50% EtOAc/Hexanes) to provide an oil (130 mg). This material converted to the title compound by the methods described in Example 9C. ^{1}H NMR (400 MHz, DMSO-d_6) δ11.78 (s, NH), 9.56 (br s, NH), 7.63 (br s, NH), 7.24 (s, 1H), 7.07 (s, 1H), 3.26 (br s, 2H), 3.16 (br t, J=9.5 Hz, 1H), 2.93 (br s, 1H), 2.18 (m, 1H), 1.97 (d, J=11.0 Hz,1H). APCI MS m/e 217.2 [(M+1)$^+$].

EXAMPLE 43

3-TRIFLUOROMETHYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE (See Grunewald, G. L.; Paradkar, V. M.; Pazhenchevsky, B.; Pleiss, M. A.; Sall, D. J.; Seibel, W. L.; Reitz, T. J. *J. Org. Chem.* 1983, 48, 2321–2327 Grunewald, G. L.; Markovich, K. M.; Sall, D. J. *J. Med. Chem.* 1987, 30, 2191–2208.)

The title compound was prepared by the methods described in Example 1 and 2 starting with 2-fluoro-6-trifluoromethylbromobenzene. ^{1}H NMR (400 MHz, CD_3OD) δ7.67–7.50 (3H), 3.65 (br s, 1H), 3.49–3.42 (m, 2H), 3.29 (s, 1H), 3.28–3.16 (m, 2H), 2.42 (m, 1H), 2.18 (d, J=11.5 Hz, 1H). APCI MS m/e 228.2 [(M+1)$^+$]. (HCl salt) mp 275–277° C. Anal. Calcd. for $C_{12}H_{12}F_3N.HCl.1/3H_2O$: C, 53.44; H, 5.11; N, 5.19. Found C, 53.73; H, 4.83; N, 5.16.

EXAMPLE 44

3-PHENYL-10-AZA-TRICYCLO[6.3.1.0^{2,7}]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 5-Fluoro-1,4-dihydro-1,4-methano-naphthalene and 5-iodo-1,4-dihydro-1,4-methano-naphthalene

(Eisch, J. J.; Burlinson, N. E. *J. Amer. Chem. Soc.* 1976, 98, 753–761. Paquette, L. A.; Cottrell, D. M.; Snow, R. A. *J. Amer. Chem. Soc.* 1977, 99, 3723–3733.)

Magnesium turnings (9.37 g, 385 mmol) were stirred in anhydrous THF (1000 mL) in a flame dried 2L 3 neck round bottom flask equipped with a non-equalizing addition funnel with a N_2 flow adapter. magnetic stirrer and efficient condenser equipped with a N_2 flow adapter. The flask was stirred and warmed to reflux by a removable heating mantle. 2,6-Difluoro-iodobenzene (0.3 g) was added followed by of 3N EtMgBr in THF (0.3 mL). The addition funnel was charged with an intimate mixture of cyclopentadiene (24.24 g, 367 mmol) and 2,6-difluoro-iodobenzene (88.0 g, 367 mmol). Small portions (~1 mL) of the intimate mixture were introduced to assist initiation (~4×). After ~15 minutes, the reaction initiated (exotherm, and vapor condensation) and heating was maintained as necessary during the addition of

the contents of the addition funnel. The reaction was then maintained at reflux for ~1 hour (no SM by GCMS).

The reaction was cooled to room temperature and quenched with H_2O (200 mL) followed by aqueous 1N HCl solution (200 mL) to dissolve the solids. Product was extracted with hexanes (4×150 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (150 mL), dried (Na_2SO_4), filtered through a Silica plug with hexanes rinse and concentrated to an oil (70 g). Chromatography on Silica gel eluting with hexanes provided two lots (9.0 and 21.0 g), which contained primarily 5-iodo-1,4-dihydro-1,4-methano-naphthalene. (TLC hexanes R_f 0.63).

B) 5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol

5-Iodo-1,4-dihydro-1,4-methano-naphthalene (20 g) and N-methyl morpholine N-oxide (17.61 g, 130 mmol) were stirred in acetone (90 mL) and H_2O (13 mL). To this was added a solution of OsO_4 (0.2 mL, 2.5% wt, solution in t-BuOH, 0.02 mmol). After 144 hours, florisil (5 g) and saturated aqueous $NaHSO_3$ solution (3 mL) were added and stirred for ½ hour. The mixture was filtered through a Celite pad and the filtrate concentrated to produce an oil which was purified by chromatography on Silica gel eluting with a gradient of hexanes to 100% EtOAc to provide a yellow solid (13.73 g). APCI MS m/e 301.1 $[(M-1)^+]$.

C) 10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

5-Iodo-1,2,3,4-tetrahydro-1,4-methano-naphthalene-2,3-diol (8.33 g, 27.6 mmol) and Et_3NBnCl (10 mg) were vigorously stirred in dichloroethane (25 mL) and H_2O (75 mL) then treated with sodium periodate (6.17 g, 29.0 mmol). After 1.5 hours, the layers were separated and the aqueous layer extracted with DCE (2×40 mL). The combined organic layer was washed with H_2O (4×30 mL) until no reaction to starch iodide paper was observed, then with saturated aqueous NaCl solution (30 mL). The organic layer was dried through a cotton plug and treated with benzyl amine (3.16 mL, 29.0 mmol) and stirred for 2 minutes then transferred to an addition funnel. This solution was added over ~10 minutes to a vigorously stirred cooled (0° C.) mixture of $NaHB(OAc)_3$ (18.72 g, 88.0 mmol) in DCE (150 mL). After addition was complete, the mixture was stirred without cooling for 2 hours. The mixture was quenched with saturated aqueous Na_2CO_3 solution (100 mL) and stirred for 1 hour, then the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with saturated aqueous NaCl solution (50 mL), dried through a cotton plug and concentrated. Chromatography on Silica gel provided an oil (6.3 g, 61%). (TLC 5% EtOAc/hexanes R_f 0.10). ^1H NMR (400 MHz, $CDCl_3$) δ7.61 (d, J=8.0 Hz, 1H), 7.28–7.22 (m, 3H), 7.13 (d, J=8.0 Hz, 1H), 6.98–6.94 (m, 3H), 3.58 (AB dd, J=14.2 Hz, 2H), 3.26 (br s, 1H), 3.21 (br s, 1H), 3.04 (br d, J=10.2 Hz, 1H), 2.83 (br d, J=10.2 Hz, 1H), 2.47 (d, J=10.0 Hz, 1H), 2.39 (d, J=10.0 Hz, 1H), 2.34 (m, 1H), 1.72 (d, J=10.5 Hz, 1H). APCI MS m/e 376.0 $[(M+1)^+]$.

D) 10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

(For a discussion, see: Miyaura, N.; Suzuki, A *Chem. Rev.* 1995, 95. 2457–2483.)

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (375.3 mg, 1.0 mmol), potassium acetate (785 mg, 8.0 mmol) and phenyl boronic acid (183 mg, 1.5 mmol) were combined in 10/1 EtOH/H_2O (5 mL). The mixture was degassed (3 vacuum/N_2 cycles), treated with tetrakis (triphenylphosphine)palladium(0) (57.5 mg, 0.05 mmol) and warmed to 90° C. for 18 h. The reaction was cooled, diluted with H_2O and extracted with Et_2O (3×50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to provide an oil (180 mg, 55%). (TLC 4% EtOAc/hexanes R_f 0.18). GCMS m/e 325 $(M)^+$.

E) 3-Phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-phenyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene was converted into the title compound utilizing the conditions described in Example 2D. (TLC 10% MeOH/CH_2Cl_2 (NH_3) R_f 0.30). (data for free base) ^1H NMR (400 MHz, $CDCl_3$) δ7.46–7.15 (8H), 3.17 (br s, 1H), 3.01 (m, 2H), 2.93 (d, J=13.0 Hz, 1H), 2.72 (dd, J=10.5,2.5 Hz, 1H), 2.63 (dd, J=10.5,2.5 Hz, 1H), 2.41 (m, 1H), 1.91 (d, J=10.5 Hz, 1H). APCI MS m/e 236.2 $[(M+1)^+]$. (HCl salt) mp 262–265° C. Anal. Calcd, for $C_{17}H_{17}N.HCl.1/3H_2O$: C, 73.26; H, 6.86 N, 5.19. Found C, 73.50; H, 6.77; N, 5.04.

EXAMPLE 45

3-HYDROXY-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$]DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

A) 10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-iodo-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3.5-triene (3.0 g, 7.99 mmol) was stirred in anhydrous THF (40 mL) at −78° C. under nitrogen and treated dropwise with n-BuLi (3.84 mL of 2.5 M soln, in hexanes, 9.59 mmol). After 10 minutes, tri-isopropylborate (4.61 mL, 20.0 mmol) was added dropwise. After ~½ hour, the reaction was poured into saturated aqueous $NaHCO_3$ solution, stirred 5 minutes and extracted with EtOAc (3×50 mL) and concentrated. The residue was dissolved in 30% Et_2O/hexanes and extracted with 1N NaOH aqueous solution (4×50 mL). The combined aqueous basic layer was treated with concentrated HCl to achieve pH 8 and extracted with EtOAc (4×25 mL), dried (Na_2SO_4) and stripped. Chromatography on Silica gel eluting first with 3% EtOAc/hexanes to remove non-polar components, then with 5% MeOH/CH_2Cl_2 provides the title compound, (TLC 25% EtOAc/hexanes R_f 0.60).

B) 10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene

10-Benzyl-3-boronic acid-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (140 mg, 0.48 mmol) dissolved in THF (5 mL) was treated with N-methylmorpholine-N-oxide (64.5 mg, 0.48 mmol) and brought to reflux for 1 hour. The reaction was concentrated and chromatographed on Silica gel to provide product. (TLC 25% EtOAc/hexanes R_f 0.18). ^1H NMR (400 MHz, $CDCl_3$) δ7.18–7.15 (3H), 7.04 (dd, J=8.0,7.0 Hz, 1H), 6.95 (m, 2H), 6.75 (d, J=7.0 Hz, 1H), 6.59 (dd, J=8.0,1.0 Hz, 1H), 3.53 (br s, OH), 3.51 (AB d, J=14.0 Hz, 2H), 3.28 (br s, 1H), 3.06 (br s, 1H), 2.91 (dd, J=8.5, 1.5 Hz, 1H), 2.79 (ddd, J=8.5,1.5,1.5 Hz, 1H), 2.42 (d, J=11.0 Hz, 1H), 2.39 (d, J=11.0 Hz, 1H), 2.23 (m, 1H), 1.65 (d, J=10.5 Hz, 1H). APCI MS m/e 266.5 $[(M+1)^+]$.

C) 3-Hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene hydrochloride

10-Benzyl-3-hydroxy-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene (160 mg, 0.60 mmol) was converted into the title compound by the methods described in Example 1D. ^1H NMR (400 MHz, $CDCl_3$) δ7.15 (dd, J=8.0,7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 3.51 (br s, 1H), 3.33–3.25 (3H), 3.16 (d, J=12.0 Hz, 1H), 3.09 (d, J=12.0 Hz, 1H), 2.29 (m, 1H), 2.02 (d, J=11.0 Hz, 1H). APCI MS m/e 175.8 $[(M+1)^+]$. (HCl salt) mp 253–255° C.

EXAMPLE 46

4,5-DIFLUORO-10-AZA-TRICYCLO[6.3.1.$0^{2,7}$] DODECA-2(7),3,5-TRIENE HYDROCHLORIDE

The title compound was prepared by the methods described in Example 1 and 2 starting with 2,4,5-trifluorobromobenzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 (t, J=8.5 Hz, 2H), 3.48–3.13 (6H), 2.38 (m, 1H), 2.11 (d, J=11.5 Hz, 1H). APCI MS m/e 196.2 [(M+1)$^+$]. (HCl salt) mp 301–303° C. Anal. Calcd. for $C_{11}H_{11}F_2N.HCl.1/6H_2O$: C, 56.30; H, 5.30; N, 5.97. Found C, 56.66; H, 5.41; N, 5.96.

EXAMPLE 47

6-ETHYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10yl)-ethanone and propionyl chloride were converted to the title compound following the procedures described in Example 30 and Goldstein, S. W.; Dambek. P. J, *J. Het. Chem.* 1990, 27, 335. ^{1}H NMR (400 MHz, CD_3OD) δ7.64 (s, 1H), 7.62 (s, 1H), 3.48 (d, J=2.5 Hz, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.20 (2H), 3.01 (q, J=7.5 Hz, 2H), 2.45 (m, 1H), 2.17 (d, J=11.5 Hz, 1H), 1.42 (t, J=7.5 Hz, 3H). APCI MS m/e 229.2 [(M+1)$^+$].

EXAMPLE 48

6-ISOPROPYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and isobutyryl chloride were converted to the title compound following the procedures described in EXAMPLE 47. (TLC 25% EtOAc/hexanes R_f 0.14). ^{1}H NMR (400 MHz, CD_3OD) δ7.65 (2H), 3.49 (br s, 2H), 3.41 (d, J=12.0 Hz, 2H), 3.33–3.19 (3H), 2.45 (m, 1H), 2.18 (d, J=11.5 Hz, 1H), 1.45 (d, J=7.0 Hz, 6H). APCI MS m/e 243.2 [(M+1)$^+$]. (HCl salt) mp 249–251° C.

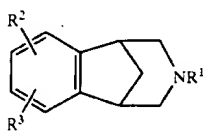
EXAMPLE 49

6-BENZYL-5-OXA-7,13-DIAZATETRACYCLO [9.3.1.$0^{2,10}$.$0^{4,8}$]PENTADECA-2(10),3,6,8-TETRAENE HYDROCHLORIDE

2,2,2-Trifluoro-1-(4-hydroxy-5-amino-10-aza-tricyclo [6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-10-yl)-ethanone and phenyl-acetyl chloride were converted to the title compound following the procedures described in EXAMPLE 47. ^{1}H NMR (400 MHz, CD_3OD) δ7.63 (s, 1H), 7.58 (s, 1H), 7.36–7.24 (5H), 4.29 (s, 2H), 3.46 (d, J=2.5 Hz, 2H), 3.39 (d, J=12.0 Hz, 2H), 3.18 (2H), 2.42 (m, 1H), 2.15 (d, J=11.5 Hz, 1H). APCI MS m/e 291.2 [(M+1)$^+$].

What is claimed is:

1. A compound of the formula



(I)

R^1 is hydrogen, $(C_1–C_6)$alkyl, unconjugate $(C_3–C_6)$ alkenyl, $XC(=O)R^{13}$, benzyl or —CH_2CH_2—O—$(C_1–C_4)$alkyl;

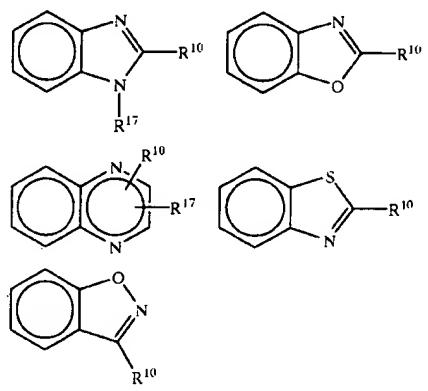
R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo rings shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from $(C_1–C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1–C_6)$alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, $(C_2–C_6)$ alkenyl, $(C_2–C_6)$alkynyl, hydroxy, amino, $(C_1–C_6)$ alkylamino and $((C_1–C_6)alkyl)_2$amino, —CO_2R^4, —$CONR^5R^6$, —$SO_2NR^7R^8$, —$C(=O)R^{13}$ and —$XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and $(C_1–C_6)$ alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—$(C_1–C_6)$ alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, $(C_1–C_6)$alkylene;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^2 and R^3, together with the benzo of formula I, form a bicyclic ring system selected from the following:



wherein R^{10} and R^{17} are selected, independently, from $(C_1–C_6)$ alkyl optionally substituted with from one to seven fluorine atoms; $(C_1–C_6)$ alkoxy optionally substituted with from one to seven fluorine atoms; $(C_2–C_6)$alkenyl, $(C_2–C_6)$ alkynyl, hydroxy, amino, $(C_1–C_6)$alkylamino and $((C_1–C_6)$ alkyl)$_2$amino, —CO_2R^4, —$CONR^5R^6$, —$SO_2NR^7R^8$, —$C(=O)R^{13}$ and —$XC(=O)R^{13}$ and wherein R^4, R^5, R^6, R^7, R^8 and R^{13} are as defined in claim 1.

3. A compound according to claim 1 selected from the group consisting of:

5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-butyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-isobutyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-neopentyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

and pharmaceutically acceptable salts thereof.

4. A compound according to claim **1** which is:

6-methyl-5-thia-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim **1** which is:

6-methyl-7-propyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

or a pharmaceutically acceptable salt thereof.

6. A compound according to claim **1** which is:

6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

or a pharmaceutically acceptable salt thereof.

7. A compound according to claim **1** which is:

6,7dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

8. A compound according to claim **1** which is:

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

9. A compound according to claim **1** which is:

14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim **1** which is:

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim **1** which is:

7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;

or a pharmaceutically acceptable salt thereof.

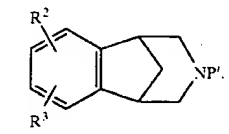
12. A pharmaceutical composition comprising an amount of a compound according to claim **1** and a pharmaceutically acceptable carrier.

13. A method for reducing nicotine addiction or aiding in the cessation or lessening of tobacco use in a mammal, comprising administering to said mammal an amount of a compound according to claim **1** that is effective in reducing nicotine addiction or aiding in the cessation or lessening of tobacco use.

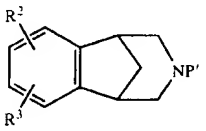
14. A method for treating a disorder or condition selected from inflammatory bowel disease, ulcerative colitis, pyoderma gangrenosum, Crohn's disease, irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions; dependencies on, or addictions to, nicotine, tobacco products, alcohol, benzodiazepines, barbiturates, opioids or cocaine; headache, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's Chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age related cognitive decline, epilepsy, petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound according to claim **1** that is effective in treating such disorder or condition.

15. A compound of the formula (I')

(I')



(I')



wherein

R^2 and R^3, together with the carbons to which they are attached, form a four to seven membered monocyclic, or ten to fourteen membered bicyclic, carbocyclic ring that can be saturated or unsaturated, wherein from one to three of the nonfused carbon atoms of said monocyclic rings, and from one to five of the carbon atoms of said bicyclic rings that are not part of the benzo ring shown in formula I, may optionally and independently be replaced by a nitrogen, oxygen or sulfur, and wherein said monocyclic and bicyclic rings may optionally be substituted with one or more substituents that are selected, independently, from (C_1–C_6) alkyl optionally substituted with from one to seven fluorine atoms; (C_1–C_6)alkoxy optionally substituted with from one to seven fluorine atoms; nitro, cyano, halo, (C_2–C_6) alkenyl, (C_2–C_6)alkynyl, hydroxy, amino, (C_1–C_6) alkylamino and ((C_1–C_6)alkyl)$_2$amino, —CO_2R^4, —$CONR^5R^6$, —$SO_2NR^7R^8$, —$C(=O)R^{13}$ and —$XC(=O)R^{13}$;

wherein each R^4, R^5, R^6, R^7, R^8 and R^{13} is selected, independently, from hydrogen and (C_1–C_6) alkyl, or R^5 and R^6, or R^7 and R^8 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1–C_6) alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; and

each X is, independently, (C_1–C_6)alkylene;

and P' is $COOR^{1o}$ wherein R^{1o} is allyl, 2,2,2-trichloroethyl or (C_1-C_6)alkyl; $—C(=O)NR^5R^o$ wherein R^5 and R^o are selected, independently, from hydrogen and (C_1-C_6) alkyl, or R^5 and R^6 together with the nitrogen to which they are attached, form a pyrrolidine, piperidine, morpholine, azetidine, piperazine, —N—(C_1-C_6)alkylpiperazine or thiomorpholine ring, or a thiomorpholine ring wherein the ring sulfur is replaced with a sulfoxide or sulfone; $—C(=O)H$, $—C(=O)(C_1-C_6)$alkyl wherein the alkyl moiety may optionally be substituted with from 1 to 3 halo atoms; benzyl, or t-butoxycarbonyl (t-Boc).

* * * * *

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
6,410,550	**$900.00**	**$0.00**	**09/402,010**	**06/25/02**	**09/28/99**	**04**	**NO**	**PAID**	**PC10030A**

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BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
14-Sep-99	Submission to FDA	Initial IND
20-Sep-99	Correspondence from FDA	Initial IND acknowledgement
22-Sep-99	Response to FDA	Response to 20-Sep-99 request for IND desk copies
13-Oct-99	Submission to FDA	Clinical
22-Oct-99	Submission to FDA	Change in Protocol
26-Jan-00	Submission to FDA	New Protocol; CMC
23-Feb-00	Submission to FDA	New Investigator; Revised FDA-1572 Form
9-Mar-00	Response to FDA	Response to FDA 1&2-May request for pk protocol and safety tables
31-Mar-00	Response to FDA	Response to FDA Request for Information; clinical agreements 21-Mar-00
5-Apr-00	Correspondence from FDA	Minutes of Phase 2 Study Protocol 1002 telecon
19-Apr-00	Response to FDA	Response to FDA 21-Mar-00 Request, Amendment to Study Protocol 1002
22-May-00	Submission to FDA	New Investigator
22-May-00	Correspondence from FDA	Comments on Phase 2 Study Protocol 1002 amendment
25-May-00	Submission to FDA	Clinical
8-Jun-00	Submission to FDA	CMC
27-Jun-00	Submission to FDA	Safety Report
29-Jun-00	Submission to FDA	New Investigator
14-Jul-00	Submission to FDA	New Protocol; New Investigator
21-Jul-00	Submission to FDA	New Investigators; CMC
18-Aug-00	Submission to FDA	New Investigator
6-Sep-00	Submission to FDA	Investigator's Brochure
29-Sep-00	Submission to FDA	Protocol Amendment; New Investigator; Toxicology
6-Oct-00	Submission to FDA	IND Annual Report
26-Oct-00	Submission to FDA	New Protocol; New Investigator; CMC
1-Nov-00	Submission to FDA	New Protocol; New Investigator; CMC
6-Dec-00	Correspondence from FDA	Recommendation for smoking status in Study 1006
12-Dec-00	Submission to FDA	Revised FDA 1572 Forms;Toxicology
9-Jan-01	Submission to FDA	Amendment to Study Protocol 1006
7-Mar-01	Submission to FDA	Revised FDA 1572 Forms;CMC
13-Mar-01	Response to FDA	Response to FDA re Study 1006 smoking status telecons 7Dec2000&22Feb2001
22-Mar-01	Submission to FDA	Revised FDA 1572 Form
6-Apr-01	Correspondence from FDA	Preclinical questions on initial IND
9-Apr-01	Submission to FDA	Toxicology
30-May-01	Submission to FDA	New Protocol, New Investigator, Chemistry, Manufacturing & Controls
7-Jun-01	Submission to FDA	Change in Protocol; Revised FDA-1572 Form
8-Jun-01	Response to FDA	FDA on review of IND and Phase 2 Program. Responses 31-Mar-00, 1-Apr-00, 25-May-00
28-Jun-01	Submission to FDA	General Correspondence: Request for Meeting to discuss Study 1002 results
16-Jul-01	Submission to FDA	New Protocol;New Investigator;Clinician's CV;Revised FDA-1572 Forms
23-Jul-01	Correspondence from FDA	Date for Type C meeting Sept 5 2001
17-Aug-01	Submission to FDA	General Correspondence: Briefing Package for Sept 5 2001 meeting
24-Aug-01	Submission to FDA	New Investigators; Toxicology
18-Sep-01	Submission to FDA	New Protocol; New Investigator; CMC

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
26-Sep-01	Correspondence from FDA	Minutes of Type C meeting Sept 5 2002
27-Sep-01	Submission to FDA	New Protocol; New Investigator; CMC
18-Oct-01	Submission to FDA	IND Annual Report
18-Oct-01	Submission to FDA	New Investigator; CMC
29-Oct-01	Submission to FDA	New Protocol; New Investigator
5-Nov-01	Submission to FDA	New Protocol; New Investigator
16-Nov-01	Submission to FDA	Meeting Minutes from 5Sept2001; New Protocol; Revised FDA-1572 Forms; CMC
20-Nov-01	Submission to FDA	New Investigators; Revised FDA 1572 Form
14-Dec-01	Submission to FDA	New Investigator; Investigator Brochure
20-Dec-01	Submission to FDA	New Protcol; New Investigator
21-Dec-01	Submission to FDA	Information amendment, Clinical
10-Jan-02	Submission to FDA	Change in Protocols; New Investigators
11-Feb-02	Submission to FDA	New Investigators
8-Mar-02	Submission to FDA	Protocol, CMC
14-Mar-02	Submission to FDA	New Protocol, Protocol Change
19-Mar-02	Submission to FDA	Change in Protocols; New Investigators
2-Apr-02	Submission to FDA	Change in Protocols; New Investigators
8-Apr-02	Submission to FDA	New Protocol; New Investigators
25-Apr-02	Submission to FDA	New Investigator;Revised FDA-1572 Forms;CMC
25-Apr-02	Submission to FDA	Protocol Change
29-Apr-02	Submission to FDA	Toxicology
2-May-02	Submission to FDA	Request for Special Protocol Assesment
7-May-02	Submission to FDA	Request for Special Protocol Assessment
22-May-02	Submission to FDA	New Investigators; Revised FDA-1572 Forms;Toxicology
5-Jun-02	Response to FDA	Response to FDA request for information 3-Jun-02, Toxicology
13-Jun-02	Correspondence from FDA	Further CAC recommendations
26-Jun-02	Submission to FDA	New Investigators, Revised FDA 1572 Forms
3-Jul-02	Submission to FDA	Request for Special Protocol Assessment, Info Amendment - Pharm/Tox
11-Jul-02	Response to FDA	9-Jul-02 FDA request for information, Pharmacology
16-Jul-02	Submission to FDA	Revised FDA 1572 Forms; Update IB
2-Aug-02	Correspondence from FDA	CAC recommendations
16-Aug-02	Submission to FDA	New Investigator, Revised FDA 1572 Forms
28-Aug-02	Submission to FDA	Protocol, New Investigator, CMC, Labels, Investogator CV
6-Sep-02	Submission to FDA	New Investigator, CMC
12-Sep-02	Submission to FDA	General Correspondence: EOP2 Meeting Request
1-Oct-02	Submission to FDA	CMC, Toxicology
4-Oct-02	Submission to FDA	New Investigator, Revised FDA 1572 Forms
21-Oct-02	Correspondence from FDA	Date for End of Phase 2 meeting
29-Oct-02	Submission to FDA	IND Annual Report
7-Nov-02	Submission to FDA	End of Phase 2 Meeting Package
8-Nov-02	Submission to FDA	Investigator's Brochure
15-Nov-02	Submission to FDA	New Protocol; Revised FDA 1572 Form; CMC
27-Nov-02	Response to FDA	Response to FDA Questions 26-Nov-02 Quit rates

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
17-Dec-02	Submission to FDA	Minutes: End-of-Phase 2 Meeting
17-Dec-02	Submission to FDA	New Investigators; CMC
3-Jan-03	Submission to FDA	General Correspondence: Response to FDA's 31Dec2002 recommendation for Study 1024
6-Feb-03	Correspondence from FDA	Minutes of End of Phase 2 meeting
6-Feb-03	Submission to FDA	Revised FDA 1572 Forms, General Correspondence: USAN Name
7-Feb-03	Submission to FDA	New Protocol Study 1035
7-Mar-03	Submission to FDA	New Investigator, January 2003 Erratum, New contact
19-Mar-03	Submission to FDA	Change in Protocol Study 1024; New Investigator
10-Apr-03	Submission to FDA	Revised FDA 1572 Form; CMC
9-May-03	Submission to FDA	Change in Protocol Study 1035; New Investigator; Revised FDA 1572 Form
3-Jun-03	Submission to FDA	Change in Protocols Studies 1018 and 1019; New Investigator; Revised FDA 1572 Form
9-Jun-03	Submission to FDA	New Protocol Study 1028, New Investigator, CMC
26-Jun-03	Submission to FDA	New Protocol Study 1036; New Investigator; Revised FDA 1572 Forms
1-Jul-03	Submission to FDA	Revised FDA 1572 Form
11-Jul-03	Submission to FDA	New Investigators
16-Jul-03	Submission to FDA	New Protocol Study 1031; New Investigator
13-Aug-03	Submission to FDA	New Investigators; Revised FDA 1572 Forms
15-Aug-03	Submission to FDA	General Correspondence Request for Meeting CMC/EOP2
21-Aug-03	Correspondence from FDA	Comments on inclusion criteria in 1028 and 1036
27-Aug-03	Submission to FDA	New Investigators, Revised FDA 1572 Forms; CMC
27-Aug-03	Submission to FDA	General Correspondence: Request for Meeting (CMC)
28-Aug-03	Response to FDA	General Correspondence - Response to Request for Information
4-Sep-03	Correspondence from FDA	Date and details for EOP2 (CMC) meeting
10-Sep-03	Submission to FDA	End of Phase 2 CMC Meeting Information: Pre-meeting Information Package for CMC
18-Sep-03	Submission to FDA	Protocol Amendments for studies 1028 & 1036, New Investigators, Revised FDA 1572
25-Sep-03	Submission to FDA	New Protocols, New Investigators
10-Oct-03	Submission to FDA	New Protocols, New Investigators, CMC
20-Oct-03	Submission to FDA	New Protocol; New Investigator
5-Nov-03	Submission to FDA	New Investigators; Revised FDA 1572 Forms; CMC
7-Nov-03	Submission to FDA	New Protocol; New Investigator
11-Nov-03	Correspondence from FDA	FDA EOP2 (CMC) minutes
13-Nov-03	Submission to FDA	IND Annual Report
2-Dec-03	Submission to FDA	New Investigators, Revised FDA 1572 Forms
9-Dec-03	Submission to FDA	Investigator's Brochure
22-Dec-03	Submission to FDA	General Correspondence: EOP2 meeeting minutes clarification; abuse liability briefing
15-Jan-04	Submission to FDA	New Investigators, Revised FDA 1572 Forms
13-Feb-04	Submission to FDA	Safety Letter
10-Mar-04	Submission to FDA	New Investigators, Revised FDA 1572 Forms, IB Addendum
22-Mar-04	Correspondence from FDA	Request for additional information re abuse potential briefing document
23-Mar-04	Submission to FDA	Information Amendment CMC
30-Mar-04	Submission to FDA	Pharmacology/Toxicology
7-Apr-04	Submission to FDA	Safety Report
13-Apr-04	Submission to FDA	Response to abuse potential questions, New Investigator, Revised FDA 1572 Forms

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
3-May-04	Submission to FDA	CMC; Revised FDA 1572 Forms
12-May-04	Submission to FDA	Safety Report
21-May-04	Submission to FDA	General Correspondence - Clinical; request for feedback on P3 narratives proposal
26-May-04	Submission to FDA	CMC
1-Jun-04	Submission to FDA	Safety Letter
22-Jun-04	Submission to FDA	Revised FDA 1572 Forms
14-Jul-04	Submission to FDA	Meeting Request to discuss CMC related NDA filing strategies
6-Aug-04	Submission to FDA	Revised FDA 1572 Forms
23-Aug-04	Submission to FDA	Safety Letter
31-Aug-04	Submission to FDA	Safety Letter
13-Sep-04	Submission to FDA	Pre meeting Information Package for CMC
21-Sep-04	Submission to FDA	New Protocol, New Investigator
28-Sep-04	Submission to FDA	New Protocols, New Investigators, CMC
19-Oct-04	Submission to FDA	IND Annual Report
20-Oct-04	Submission to FDA	General Correspondence: Tradename proposal
2-Nov-04	Submission to FDA	Toxicology, Clinical Study Report, Revised FDA 1572 Forms
5-Nov-04	Submission to FDA	Follow up Safety Letter
10-Nov-04	Response to FDA	General Correspondence: Summary of Agreements from Type C CMC Meeting
9-Dec-04	Submission to FDA	New Protocol, New Investigator, CMC, Revised FDA 1572 Forms
21-Dec-04	Correspondence from FDA	Meeting Minutes 14Oct04
22-Dec-04	Response to FDA	responses to issues raised in 13Apr04 assessment of amendment dated 13apr04 re
6-Jan-05	Submission to FDA	New Investigator, New Protocol
21-Jan-05	Response to FDA	Comments on FDA meeting minutes re comparability protocols from 14Oct04 CMC
4-Feb-05	Submission to FDA	Toxicology reports, Protocol Amendment, New Protocol, New Investigator, Revised FDA
11-Feb-05	Submission to FDA	Clinical, CMC
25-Feb-05	Submission to FDA	Request for a pre-NDA meeting
11-Mar-05	Submission to FDA	New Investigator, CMC
23-Mar-05	Correspondence from FDA	Letter confirming date of Pre-NDA meeting
1-Apr-05	Submission to FDA	Safety Letter
5-Apr-05	Submission to FDA	Protocol Amendment - New Investigators; Revised FDA 1572 Form
18-Apr-05	Submission to FDA	Comparability Protocol
22-Apr-05	Submission to FDA	Information amendment: Statistical analysis plan
22-Apr-05	Submission to FDA	Information Amendment Clinical
5-May-05	Submission to FDA	New Investigators, Revised FDA 1572 Forms
6-May-05	Submission to FDA	General Correspondence statistical analysis plan for Study 1039
10-May-05	Submission to FDA	Briefing Document for Pre-NDA meeting
11-May-05	Response to FDA	Response to FDA questions related to Statistical Analysis Plan
17-May-05	Submission to FDA	New Protocol, New Investigator, CMC, Revised FDA 1572 Forms
27-May-05	Submission to FDA	Safety Letter
20-Jun-05	Response to FDA	Response to FDA Request for Information from the Pre-NDA meeting
22-Jun-05	Submission to FDA	New Investigator, CMC, Revised FDA 1572 Forms
30-Jun-05	Submission to FDA	Comparability Protocol
3-Aug-05	Submission to FDA	Proposed Comprehensive Quality Overview Summary for the Varenicline Tartrate NDA

BRIEF DESCRIPTION OF REPRESENTATIVE SIGNIFICANT ACTIVITIES DURING THE REGULATORY PERIOD FOR CHANTIX™ (varenicline) Tablets

Date	Activity	Comments
3-Aug-05	Submission to FDA	Protocol Change
23-Sep-05	Submission to FDA	General Correspondence -PRO document
4-Oct-05	Submission to FDA	General Correspondence: Request for meeting with Office of New Drug Chemistry
11-Oct-05	Submission to FDA	New Protocol, CMC, Revised FDA 1572 Forms
24-Oct-05	Submission to FDA	General Correspondence: Feedback on FDA minutes from 18 Aug 2005 Abuse Liability
9-Nov-05	Submission to FDA	New Drug Application
21-Nov-05	Submission to FDA	General Correspondence: NDA Safety Update Proposal
2-Dec-05	Submission to FDA	Annual Report
8-Dec-05	Submission to FDA	New Protocols; CMC
6-Jan-06	Correspondence from FDA	Meeting minutes from 9Jun05 Pre-NDA meeting
13-Jan-06	Submission to FDA	Type C Meeting Request
27-Jan-06	Submission to FDA	New Investigators, Revised FDA 1572 Forms, Clinical
3-Feb-06	Response to FDA	FDA Query received 25Jan06 related to report links and study locations
7-Feb-06	Submission to FDA	Stability Update
9-Feb-06	Submission to FDA	3 mo Safety Udate
13-Feb-06	Response to FDA	FDA Query received 27Jan06 related to Qualifying Procedures and report datasets
3-Mar-06	Response to FDA	FDA request received 28Feb06 for reconciliation and data
3-Mar-06	Submission to FDA	Request for pre-approval importation
10-Mar-06	Submission to FDA	New protocol, New Investigators and Revised FDA 1572 Forms
8-Mar-06	Response to FDA	FDA request received 6Mar06 for updated CTD sections
10-Mar-06	Response to FDA	FDA request received 3Mar09 for histories and measures tables
14-Mar-06	Response to FDA	FDA letter received 6Mar06 regarding Trade Name
14-Mar-06	Response to FDA	FDA request received 3Mar06 dependence
14-Mar-06	Response to FDA	FDA request received 7Mar06 for AE tables
15-Mar-06	Response to FDA	FDA request received 10Mar06 for QT data
23-Mar-06	Response to FDA	FDA request received 20Mar06 SAEs
24-Mar-06	Response to FDA	FDA request received 21Mar06 for different presentation of table
27-Mar-06	Response to FDA	FDA request received 23Mar06 for data
29-Mar-06	Response to FDA	FDA Query received 20Mar06 related to interpretation of CPK values
31-Mar-06	Response to FDA	FDA request received 27Mar06 for new AE data
31-Mar-06	Response to FDA	FDA request received 30Mar06 for data
7-Apr-06	Response to FDA	FDA request received 31Mar06 for data tables
11-Apr-06	Response to FDA	Quality Queries
20-Apr-06	Response to FDA	Quality Queries Received 24Feb and 13Mar06
1-May-06	Response to FDA	Follow to 27Apr06 telecon related to dosing
4-May-06	Response to FDA	Quality Queries 21April and May4,06
9-May-06	Response to FDA	Quality Queries 05May06
10-May-06	Correspondence from FDA	FDA letter received May 5 and telecon May 9 regarding package label
11-May-06	Submission to FDA	Final Printed Label and Promotional Materials